Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Management of Gout*

Draft review available for public comment from June 25, 2015 to July 24, 2015.

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Quality of Report	Superior	Thank you
TEP Reviewer #1	Quality of Report	Superior	Thank you
Peer Reviewer #2	Quality of Report	Superior	Thank you
TEP Reviewer #2	Quality of Report	Superior	Thank you
Peer Reviewer #3	Quality of Report	Superior	Thank you
TEP Reviewer #3	Quality of Report	Superior	Thank you
TEP Reviewer #4	Quality of Report	Fair	Thank you
TEP Reviewer #5	Quality of Report	Superior	Thank you
Peer Reviewer #1	General	This is a quite readable and clinically relevant report. Even though there are a limited number of 'new' findings in the treatment of this condition, the practice community will find this useful.	Thank you
TEP Reviewer #1	General	this is an amazing work, the review of the recent literature, development of the KQ and the systematic methodology used to answer the questions is impressive. the target population was defined early in the paper.	Thank you

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	I will refer to the pages by using the numbers found at the top of each individual page General comments: This paper represents an outstanding amount of work in search and summarizing the current literature. It is a sound and very useful basis from which to work from in order to develop and inform recommendations for primary care (or in fact, any other setting). One concern is that the summarizing of the evidence of each individual SLR many times takes up an important amount of time and space, both of which increase with the amount of retrieved literature. Here five key questions are presented, and each one consists of several sub-questions which are answered by one or several SLRs. In all, I find that for some areas I would like further information to be presented (i.e. RoB assessments). But the paper provides a clear report of very good quality.	ROB assessments are provided for each included SR and each included clinical trial not otherwise included in a SR.
TEP Reviewer #2	General	The writing group should be commended on draft summary of this report. This is clearly the culmination of substantial efforts, following a rigorous methodology, and will undoubtedly serve as a tremendous resource in gout management moving forward. Specifically, the review is quite comprehensive in scope and will be an important resource for both guideline groups and gout researchers identifying a research agenda.	Thank you
TEP Reviewer #2	General	The target audience is very clearly defined and the key questions are explicity stated.	Thank you
Peer Reviewer #3	General	1. The typical hierarchy of evidence strength does not neatly fit for gout. While the grading of the evidence is reasonable based on the typical hierarchy, many gout experts will take issue with the statement that "the strength of evidence is low that treating to a specific target serum urate level reduces the risk of gout attacks." There are biochemical experiments with known levels of pharmacokinetic solubility for uric acid in the joint. These data have always dictated the importance of reducing serum uric acid below 6.8mg/dl to achieve negative uric acid balance. Serum uric acid levels below 6mg/dl have traditionally been the target for uric acid lowering treatments. While I agree that the evidence from treatment trials is lacking, its not clear that the strength of evidence is really "low" for this target.	While we agree with this statement of the rationale for a SoE of greater than "Low" other stakeholders have argued that without any hypothesis tests of a treat-to-target strategy the SoE cannot even rise to "Low", it should be "insufficient". We have explained our rationale for grading this as "Low", and acknowledge that other experts may view it differently.
Peer Reviewer #3	General	2. Table A (pg. ES-2) may have some inaccuracies. I believe that URL pharma sold Colcrys to Takeda several years ago. I also don't believe that Savient is still in existence but maybe they exist in some form.	Yes, we have revised the name of the manufacturer of Colcrys to Takeda and Savient Pharmaceuticals to Crealta.
Peer Reviewer #3	General	3. Some will take issue with the statement that evidence does not support the fact that febuxostat reduces tophus burden. The pivotal trial by Becker et al (NEJM, 2005) showed tophus reduction. I believe that several other smaller trials with other agents (?pegloticase) has also shown similar results.	That sentence and conclusion was not meant to refer to effectiveness reducing tophi, but rather differential effectiveness of ULT based on presence or absence of tophi at baseline. We revised the sentence.

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Peer Reviewer #3	General	4. The statement that "Insufficient evidence supports or refutes that monitoring serum urate improves outcomes" seems to fly in the face of the understanding noted above that serum uric acid must be reduced below 6.8mg/dl to reduce the crystallization of uric acid in joints. The absence of randomized trial evidence does not mean something has weak evidence.	We agree that if the reviewer accepts that treating to a specific target is appropriate therapy, then monitoring serum urate should be rated higher than "insufficient". However, as we judged the SoE for a treat to target strategy to be "Low", without a hypothesis testing study supporting monitoring we could not judge the SoE for monitoring as anything other than insufficient.
Peer Reviewer #3	General	5. The double negative expressed in the following statement is very confusing. Please consider rephrasing. "There is low strength of evidence that discontinuing urate lowering therapy in gout patients who completed five years of ULT therapy that kept serum urate levels < 7mg/dl, and in whom subsequent annual serum urate levels (off of ULT) stayed < 7mg/dl, did not result in an increased risk of acute gout attacks."	We have revised this sentence.
Peer Reviewer #3	General	6. I was surprised by the finding that HLA-B5801 did not help stratify patients at increased risk for allopurinol hypersensitivity (AH). This finding seems pretty strong based on the literature that I am aware of. I recognize that this finding is particularly relevant to Asian populations where this allele is more common. However, the RR of AH is very elevated for persons with this allele.	The sentence is not that it did not help, but rather whether studies have stratified results based on this HLA allele. We added evidence to the Harms section about the association of this HLA allele and allopurinol harms as we agree with the reviewer that there is an association and it is worth studying whether allopurinol harms can be avoided by testing high risk populations for HLA-B5801 We emphasized this gap in the “research gaps” section.
TEP Reviewer #3	General	The target population and audience is explicitly defined. The key questions are appropriate for the most part, except for the question regarding stopping ULT, which, in my personal opinion, is not an appropriate focus for PCPs, where management of gout overall is not great.	We understand the reviewer concerns but we developed key questions using an open process involving public, various stakeholder groups including PCPs, gout specialists and the AHRQ representatives.

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TEP Reviewer #3	General	I think it would be useful to have more details regarding strength of evidence (SoE) considerations because some of the designations appear to be contrary to the actual quality of the evidence (e.g., some are said to be 'strong' despite the RCTs they are based upon being of low quality or having used inappropriate comparators, etc., or the study sample was not subjects with gout).	We have expanded our explanation of how SoE was assessed and written text for each conclusion about the factors leading to SoE. Grading the Strength of the Body of Evidence for Each Key Question explains our method of assessing SoE for this review.
TEP Reviewer #3	General	I would strongly advocate for avoidance of the term 'chronic gout' as it implies that ULT should only be used once gout becomes 'chronic'. The Rheumatology community is moving away from characterizing conditions as having those types of phases because treatment is the same at the early stages of disease as it is when the disease has become more severe. It would be akin to talking about 'chronic diabetes'. If a patient progresses to 'chronic gout', it simply indicates that the patient has been inadequately managed, similar to a patient with rheumatoid arthritis progressing to erosions – the disease was not adequately managed prior to developing erosions.	The term "chronic gout" was set originally at the time of Topic Nomination, was vetted by Key Informants during the Topic Refinement process, was vetted again during the public posting of the protocol, and cannot be changed now. Furthermore the term "chronic gout" is used in the literature (for example, in the 2014 Cochrane review co-authored by Rachelle Buchbinder, Claire Bombardier, and other noted rheumatologists).

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TEP Reviewer #3	General	It seems that a major contentious issue is about the SoE regarding a treat-to-target threshold. While I understand the reasoning (i.e., there has been no RCT testing different thresholds), the recommendations seem to conflate the specific target threshold as having a low SoE with the actual important clinical value of reducing serum urate. The message seems to be mixed and confused, and I'm concerned that an appropriate message will not be received by PCPs about the importance of lowering serum urate. It also seems that the authors have not considered the fact that the mean serum urate in US adults according to NHANEs is actually 5.48mg/dL. Thus, the theoretical concern about reducing serum urate to 6mg/dL or below has not acknowledged the fact that the mean levels in US adults is actually <6mg/dL. There doesn't, therefore, seem to be a major compelling supportive argument for the concern raised about altering the benefit:risk ratio when attempting to lower serum urate to 6mg/dL.	We provided explanation in the report. A treat-to-target approach would require RCT level evidence of that strategy in order to be considered high strength evidence. Diabetes, hypertension, and hyperlipidemia all also had strong observational evidence supporting associations with various adverse outcomes, had RCT evidence showing that lowering A1C, blood pressure, and LDL resulted in improved outcomes, all had one-size-fits-all treat-to-target management strategies advocated by respected professional societies, and all three treat-to-target strategies, when actually tested in RCTs, were found to produce less benefit and more harm than predicted. Therefore, we judge that, in gout, a treat-to-target strategy will require RCT level of evidence for support before this EPC can rate it as strong evidence. The concern about lowering SUA to less than 6 is not the physiologic effects on the body but rather the increased risk of side effects, monitoring, and time associated with intensified treatment.
TEP Reviewer #4	General	Please consider modifying the title to be Nutrition Therapy and Lifestyle Management versus "Dietary" in the title and throughout the text of the report.	The term "Dietary" is used in the key questions as they were finalized during the topic refinement phase of this project with different stakeholders, and we will continue to use it in this report.
TEP Reviewer #5	General	First, the authors deserve congratulations for producing a very well-organized, well-written, and clinically relevant review. The few comments below, while general, might apply more to some sections than to others.	Thank you

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TEP Reviewer #5	General	It was not readily apparent to me whether you included only RCTs when considering original research studies, or under which circumstances you also considered papers describing other kinds of study designs (e.g. quasi-experimental methods). Eventually I found an answer in the methods, but it's sort of buried in PICOTs boilerplate. It might be helpful to readers who are not "systematic review professionals" to include a couple of sentences under a more prominent heading about what kinds of studies were/weren't considered and why. It would seem to me that where RCT data is lacking, one has to do due diligence in considering other kinds of studies.	We added a section at the beginning of the methods on "Searching for Evidence" and provided information on types of studies included in the SR
TEP Reviewer #5	General	This might be a stylistic preference, but I would find it useful if you included a paragraph or two describing the types of outcomes (e.g. not just "joint swelling and tenderness" but what were studies actually using as an outcome?) for each of the key questions (as applicable). When I read any scientific paper, I ask myself early on "do I care about this?" And without knowing whether the original studies had clinically meaningful outcomes, it is hard to answer this question (understood that some of this is in the tables).	We provided very detailed information in Table 4 on the details of reported outcomes by each included study.
TEP Reviewer #5	General	A general comment about how you deal with power issues (i.e. "lack of evidence for efficacy" vs. "evidence of no efficacy."): In general, I think that you could be a little bit crisper with how you deal with this distinction in your descriptions of the evidence. As it stands some of the summaries seem to be "lossy" in that there is probably readily available information in the existing studies which would help readers better understand the degree to which there is evidence of lack of efficacy, if you presented it or took one additional step to interpret it. For example, on page 20 you mention that with regard to studies comparing two NSAIDs, "only two studies enrolled more than 100 subjects." But given that this is not a mortality or grave disability outcome, 100 (or 178) subjects might tell us a lot. It is hard for most readers to look at a number of subjects and eyeball the power, so why not do it for them (e.g. by stating the 95% CI for the difference, or by describing the certainty of no effect in clinical terms)? Doing so would allow the reader to draw his/her own conclusions.	We are not going to calculate the power for all 16 RCTs identified as NSAID vs. NSAID, particularly as it was a consistent finding that there were no differences in effect between NSAIDs and that this result is compatible with the conclusions of studies of NSAIDs in other conditions, e.g., there are no differences in clinical effectiveness. The text already says in the summary of Key Points that we consider the evidence Moderate that there is no clinical difference in effectiveness. We added to the SoE description the factors we used in judging the SoE as moderate.

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TEP Reviewer #5	General	Comparative effectiveness It is surprising that the comparative effectiveness (both in terms of salutary and adverse effects) is not explicitly defined as a key question. As you allude to in the discussion section, for a patient presenting to primary care with an acute gouty attack, the relevant question for the clinician is almost never "should I treat with anything or nothing?" but rather, "which of the available treatments should I use?" or "which of the available treatments will provide the most rapid relief with the fewest side effects?" From my experience, the most commonly asked question in the acute care setting is NSAID vs. colchicine, followed by (NSAID or colchicine) vs. corticosteroid, followed by (one NSAID) vs. (another NSAID). On that last point, believe it or not, there are still many clinicians who prescribe indomethacin specifically for gout (but in no other circumstance). While you do cite comparative effectiveness studies on page 20, you might want to consider addressing this issue in the executive summary and otherwise highlighting it. Furthermore, NSAIDs vs. Colchicine should be explicitly mentioned, even if to say that there has been no high quality study comparing the efficacy of these drugs. Consider including under the "Research gaps" heading.	We don't think this is a major research gap. The evidence supports all of these as being of similar (if not exactly the same) effectiveness and the side effect profiles of each of these courses of therapy are well known to most primary care physicians. While precise estimates of comparativeness aren't known, we do not judge that research resources would be best put to making what is known about treating acute gout more precise. We judge these resources would be better put to the questions we stated in our Research Gaps section.
TEP Reviewer #5	General	The question of comparative drug toxicity also deserves more explicit and systematic mention, even if to say that it is outside the scope of this review (note that it is not really necessary to look only at side effects in the treatment of gout, per se. It wouldn't be much of a leap of faith to use data on drug toxicity in other clinical settings so long as the dose, duration, and population were similar). Indeed, if available evidence suggests, for example, that NSAIDS and colchicine (or ibuprofen and indomethacin) have equal efficacy, then the next question should be whether or not they are equally safe. Consideration should be given to reports of rare but serious events linked to particular drugs (e.g. aplastic anemia, colchicine).	Reviewing the comparative harms of these drugs outside of gout is beyond the scope of this review. We do summarize data from other sources on this topic, which includes rare effects for NSAIDs. We have added similar sentences for colchicine.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #6	General	1. I find the term "chronic gout' inappropriate, as it misrepresents the nature of the biology and clinical spectrum of gout, and could mislead clinical decision-making in gout care. Gout is a "chronic" condition from the time of onset, similar to diabetes or hypertension. Gout flares ("acute gout") are just a key feature of this chronic condition. If gout is left un-intervened (e.g., with risk factor management or medications), the flare frequency often increases with ongoing urate pool enlargement and development of intra- and extra-articular tophi that lead to joint destruction and limitations as well as functional decline. I think that the authors' use of "chronic gout" to reflect this advanced stage of gout that would also be indicated for urate lowering therapy (ULT) according to all published gout care guidelines. Again, the indication includes frequent gout as well as tophaceous gout (clinically apparent or intra-articular, thus not palpable by regular PE). I would modify the term to reflect this biology and clinical spectrum of gout.	We recognize the difficulties with nomenclature here. However, "chronic gout" was set originally at the time of Topic Nomination, was vetted by Key Informants during the Topic Refinement process, was vetted again during the public posting of the protocol, and cannot be changed now. Moreover, cohort data show that as many as 30% of patients with an incident gout attack never have any subsequent attack over a period up to 12 years. Classifying such patients as having a "chronic condition" seems inappropriate. Lastly, the term "chronic gout" is used in the literature and for example, in the 2014 Cochrane review co-authored by Rachelle Buchbinder, Claire Bombardier, and other noted rheumatologists.
TEP Reviewer #6	General	2. The causal relationship between serum uric acid levels and gout flares is well established at least in the rheumatology field and FDA, based on its clear underlying chemistry and biology as well as obvious anecdotal observations in clinical gout care practice supported by numerous observational studies, including extension studies of RCTs. This is the reason why the FDA accepted the target serum uric acid (SUA) levels (as opposed to gout flare reduction) as their primary end-points for FDA approval.	We agree that lowering of SUA would have reduced gout attacks, based on some evidence although this has never been demonstrated in an RCT. However, patient clinical symptoms are also an important outcome.

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TEP Reviewer #6	General	3. Related to #2 above as well as to the strengths of evidence (SoE) about a treat-to-target approach in gout care, I highly recommend that the authors carefully review one of the excluded references (Rees et al, Ann Rheum Dis. 2013 Jun;72(6):826-30). This is an open label prospective study of 100 gout patients, which clearly demonstrated the effectiveness of TTT on the flare outcomes in addition to an extremely high level of achieving target levels of serum uric acid (SUA) levels over one year. Although the trial was open-label without a control group, the effect sizes were large enough to overcome any potential regression-to-the-mean or placebo effects (more than 90% of patients to achieve the primary treatment target of SUA < 6mg/dL and 85% to achieve SUA < 5mg/dL), which are considerably higher that of febuxostat, the new FDA approved ULT. The flare rate before the trial was ~100 per 3 months (calculated based on Table 1 data), which became 68, 61, 49, and 35 in the subsequent quarters of the 1-year trial period. Notably, only 4% of trial participants received flare prophylaxis therapy, as the investigators used a low-dose initiation incremental escalation approach that the 2012 ACR criteria recommended. Based on this trial, there is an ongoing RCT in the primary care population and so far the interim results are showing very similar efficacy to that of the open label trial. This is exactly what we observe in well-managed gout care practice, which is again why the FDA agreed to accept the urate-lowering anti-gout medication based on its capacity to achieve the target SUA of <6mg/dL. Further, rheumatologists know that gout is a curable disease with appropriate urate-lowering therapy, and now this ongoing RCT seems to be proving that point in a GP care setting.	We have reviewed this article. It was rejected for inclusion as evidence for effectiveness since, as the reviewer notes, it is not an RCT, as specified in the PICOTs. We can't follow the reviewer's interpretation of the data presented in this study. We agree with the interpretation that almost all patients got below a threshold for serum urate. But we can't follow the reviewer's description of the clinical effects of this. In Table 1, the prior frequency of acute attacks is listed as a mean of 4 per year. The text of the results says that "in study completers, the mean number of self-reported attacks reduced to 2.4 (SD 2.3)." So 4 attacks per year reduced to 2.4 attacks per year, and unfortunately no statistical testing was done to see whether this was statistically different or not. Furthermore, the sample size for this latter number is not presented - is it the 96 patients (91%) listed as "completing the 12 month follow-up"? Table 3 does present data that seem to support the TTT hypothesis, but it is limited by 1) again not knowing the denominator to be able to calculate an attack rate; and 2) the footnote saying that 35% of patients reported either no change in the number of attacks or an increase in the number of attacks from the prior year. So not all patients are benefiting equally and some are being harmed. Lastly, this paper does not report possible harms in a satisfactory way. It reports that 3 patients withdrew due to side effects, but that is not the same as reporting all the side effects that occurred, and is

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			certainly underpowered to assess the risk of the feared side effect of DRESS. So, the best-case scenario for this study is that it supports a TTT strategy as giving a person a 2-out-of-3 chance for reduced acute gout attacks, a 1-in-5 chance of more gout attacks, with an unknown increased risk of adverse events. To us this does not sound like evidence that can support a strong recommendation in favor of a TTT strategy. We await the results of the listed RCT with interest. Our expectation is that a TTT strategy is going to produce, over time, fewer gout attacks (e.g., the reviewer's statement about the interim analysis showing "similar efficacy"). What we don't know is what are the side effects necessary to get all or nearly all the patients to the threshold, and whether or not there are going to be any unanticipated effects that can't be predicted from existing non-TTT RCTs or observational studies.
TEP Reviewer #6	General	4. In terms of the evidence for the efficacy of Vitamin C supplementation, a Cochrane review evaluation on the evidence of Vitamin C supplementation was fairly done in my view, and thus adopting that result in your review was reasonable as you did.	We have moved the description of studies that assess nutritional risk factors for gout or high serum urate to the introductory chapter; the review on vitamin C is summarized in that section.
TEP Reviewer #6	General	5. I agree that potential discontinuation ("drug holiday") of urate-lowering therapy after effective treatment is an intriguing idea, given the polypharmacy of typical gout patients (for their multiple comorbidities). As more potent anti-gout agents become available in the field, this topic deserves its due attention. However, I also think that it should be sufficiently emphasized that this attempt can only be considered after effective management of both SUA levels and gout flares for a durable time. Otherwise, this discussion carries some potential to hinder fixing the ongoing suboptimal gout care that has been documented in many studies.	We have tried to state the results of the Perez-Ruiz cohort as carefully as possible, to emphasize these points.

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TEP Reviewer #6	Abstract	1. Conclusion: I would strongly consider removing or modifying the third sentence, given the well-established causal relationship between serum uric acid levels and the risk of flares (see my General Comments 2 and 3). This is where almost all rheumatologists and FDA feel there is no need for "direct" demonstration as this is felt to be an unequivocal scientific fact (such as the presence of gravity or the sun rising from the east), although it may not appear so to PCPs. I suspect that this difference rises from the level of background knowledge and clinical experience with the condition.	We have modified this sentence to indicate that what remains to be demonstrated is the balance between long term benefits and harms.
TEP Reviewer #6	Abstract	2. What is the evidence to support the last sentence of the conclusion "Patient preferences and other clinical circumstances....". Is this a general statement that would apply to most chronic conditions? As we are dissecting detailed levels of evidence to each point, certainly such a general conclusion line seems somewhat unexpected and not supported by 'direct' evidence either?	This statement may apply to other chronic conditions, and we feel it is justified including here since clinical circumstances such as the presence of chronic kidney disease and diabetes can influence the treatment choices for acute gout attacks and patient preferences for different outcomes can influence the treatment of chronic gout (e.g., taking a long term medication to lower serum urate, with the concomitant risks involved versus the likely decreased risk in acute gout flare and the as-yet-unproven decreased risk of other outcomes.
TEP Reviewer #6	Analytic Frameworks	I have an extremely high level concern using the term “chronic gout” as I explained in my General Comment #1.	The term "chronic gout" was set originally at the time of Topic Nomination, was vetted by Key Informants during the Topic Refinement process, was vetted again during the public posting of the protocol, and cannot be changed now. Furthermore the term "chronic gout" is used in the literature (for example, in the 2014 Cochrane review co-authored by Rachelle Buchbinder, Claire Bombardier, and other noted rheumatologists).
TEP Reviewer #6	Background	1. ES-2, line 15: Regarding the management that is discussed about gout (as opposed to “chronic gout”). Please see my General Comment #1.	No response necessary

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TEP Reviewer #6	Background	2. ES-2, line 19: Would remove smoking cessation, which may actually decrease the risk of gout according to several epidemiologic studies. Regardless, there is no recommendation about smoking in relation to gout or hyperuricemia.	We have removed smoking cessation from the list of interventions of interest.
TEP Reviewer #6	Background	3. I would re-organize Table A into a heading of anti-inflammatory agents for gout attacks and another heading of urate-lowering agents.	We have reorganized Table A and Table 1 in the main text as the reviewer suggested.
TEP Reviewer #6	Background	4. Table A: Colchicine is now manufactured by Takeda	Thank you. We have corrected the name of the manufacturer to Takeda.
TEP Reviewer #6	Findings	1. ES-10, line 40: I find it very difficult to be convinced how ACTH was determined to have a high strength of evidence, given the data available.	This is explained in the text: ACTH acts to increase the body's production of steroids. We judged steroids to be high SoE. However, as the two equivalence trials for ACTH were both judged to be at high risk of bias and steroids had three low risk of bias equivalence trials, we downgraded the ACTH SoE to moderate.
TEP Reviewer #6	Findings	2. ES-11, line 32: As I mentioned in my General Comment #4, I agree with the Cochrane review on the Vitamin C data. That systematic review also discusses the limitations of another small study by Stamp et al. 2013.	Yes, we have decided to include the two original studies from the Cochrane review(s) rather than the reviews themselves. We agree with Andres and colleagues that the Stamp study has moderate-to-high risk of bias and we have changed the strength of evidence for a conclusion regarding vitamin E to insufficient
TEP Reviewer #6	Findings	3. ES-13, line 5: I am not sure how monitoring serum urate would need any evidence to be recommended. Once we accept that we need to treat SUA to low enough, then the level obviously needs to be followed. It would be analogous to checking glucose and HbA1c levels when our patients are on anti-diabetic agents. Even though we might not opt for a TTT approach, if we don't check SUA at all, we may well be exposing our patients to ULT and not achieving any benefits from the medication.	We acknowledge the appeal of this logical argument and have added it to the text for the summary of KQ 4B in the main report.
Peer Reviewer #1	Introduction	ES-1: Good spot to mention role of medications as risk factor for gout. Thiazides are often implicated, but the risk is overall low. while I know this is not a major aspect of the report, worth mentioning.	We have added this

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Peer Reviewer #1	Introduction	ES-2: Although uric acid renal stones may be beyond the scope of the paper, they are more common in patients with gout, aren't they? If they are not in scope, tell the reader here.	Renal stones were within scope, but no placebo-controlled treatment RCTs reported on this outcome.
Peer Reviewer #1	Introduction	Another issue that readers may wonder about is the related issue regarding whether or when to institute uric acid lowering therapy in asymptomatic hyperuricemia. If its out of scope, tell us in the introduction.	The concept of "asymptomatic hyperuricemia" is not agreed by all authorities, some of whom consider ultrasound assessment of uric acid in joints to be a "symptom". However, asymptomatic hyperuricemia", meaning the identification of included patients as those with elevated sUA but no symptoms of gout, was not within the scope of this systematic review.
TEP Reviewer #1	Introduction	ok	No response necessary
Peer Reviewer #2	Introduction	Page 33, first par: It is yet to be clarified (although given gout pathogenesis, it is likely) if asymtpomatic hyperuricemia with deposits is, in fact, gout, albeit at a pre-clinical stage (Dalbeth et al. ARD) Page 33, subsections acute gouty arthritis and chronic gout. The division between acute and chronic gout, although widely used always appears to me confusing. By acute gouty arthritis is normally used for the short episodes (1-2 weeks) of inflammation that occur in (virtually all) patients with gout. However the concept of chronic gout is less clear-cut. Some people refer to the concept of gout as a chronic disease, and linked to that, to ULT and flare prophylaxis ?). However, then these are not phases (as referred to in clinical presentation and management), as a patient with acute gout, will also have chronic gout from the first flare. Other authors refer to the persistent inflammation that will develop in some patients with long-standing and untreated gout. Then, we can talk about phases as this is (usually) a second phase after intercritical gout. But this does not seem to be the concept that is presented here. A clear definition of what will be considered chronic gout in this review would help.	The concepts of acute gout and chronic gout was set originally at the time of Topic Nomination, was vetted by Key Informants during the Topic Refinement process, was vetted again during the public posting of the protocol, and cannot be changed now. The text states on part 2 that "..acute episodes may increase in frequency and duration overtime and lead to the development of chronic gout." We do not agree that having had a first acute gout attack automatically defines a patient to have chronic gout, as the Mayo Clinic cohort showed that 30% of patients who had a 1st gout attack had no recurrences in 12.9 years of follow-up, this period of time cannot be considered by us to constitute "chronic gout".
TEP Reviewer #2	Introduction	The introduction sets the stage nicely and I have no specific comments / critiques in regards to this section of the report.	Thank you

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Introduction	Clear	Thank you
TEP Reviewer #3	Introduction	These comments are for the Executive Summary: Abstract: • The authors indicate that there is a high strength of evidence to support that ULT reduces serum urate level, but that the SoE for treating to a specific SUA target level is low given lack of a specific RCT. However, there is good biological rationale, and is recommended by all Rheumatology organizations worldwide. In other instances, the authors have given high SoE based on biological rationale, while in other instances, they have not. This inconsistency is a bit puzzling.	As explained in the report, a treat-to-target approach would require RCT level evidence of that strategy in order to be considered high strength evidence. Diabetes, hypertension, and hyperlipidemia all also had strong observational evidence supporting associations with various adverse outcomes, had RCT evidence showing that lowering A1C, blood pressure, and LDL resulted in improved outcomes, all had one-size-fits-all treat-to-target management strategies advocated by respected professional societies, and all three treat-to-target strategies, when actually tested in RCTs, were found to produce less benefit and more harm than predicted. Therefore, we judge that, in gout, a treat-to-target strategy will require RCT level of evidence for support before this EPC can rate it as strong evidence.
TEP Reviewer #3	Introduction	Abstract: • The conclusion about ULT initiation being a risk factor for gout flare should be moderated (this is mitigated by appropriate prophylaxis); the reason that a strong demonstration of reduced flares isn't available isn't just the increase in flares in the first few months of ULT initiation, but also because trials have not been of long enough duration, though open-label extension studies have demonstrated this. The true benefits of flare reduction are typically noted after the first year of treatment.	We have modified this sentence in the abstract.
TEP Reviewer #3	Introduction	Background: • In addition to stating that gout is the most common inflammatory arthritis, it should indicate that 8.3 million US adults have gout; this would put how common this condition is into appropriate context	We have added this sentence in the background.
TEP Reviewer #3	Introduction	Background: • ES-1, line 55: the description of joints involved should remove the word 'potentially' as it is quite common that other joints are involved. The lack of understanding by PCPs that gout can affect joints other than the 1st MTP often leads to missing the diagnosis of gout.	We have changed "potentially" to "may involve".

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TEP Reviewer #3	Introduction	Background: • ES-2, line 15: the management being discussed here isn't just about the management of 'chronic' gout, but rather of gout. (the terminology being used here is akin to talking about 'chronic diabetes' – one would not wait until the complications of diabetes before controlling blood glucose). As such, this should be a separate section about Management, and the term 'chronic' should be removed (line 15, line 27) since it implies that management only needs to begin once gout becomes 'chronic'. This should simply be about managing hyperuricemia in patients with gout. As well, the authors are mixing IL-1B antagonists with the discussion of ULT. The IL-1 antagonists should be discussed as the treatments for gout; they are not used to lower urate.	The term "chronic gout" was set originally at the time of Topic Nomination, was vetted by Key Informants during the Topic Refinement process, was vetted again during the public posting of the protocol, and cannot be changed now. Furthermore the term "chronic gout" is used in the literature (for example, in the 2014 Cochrane review co-authored by Rachelle Buchbinder, Claire Bombardier, and other noted rheumatologists).
TEP Reviewer #3	Introduction	Background: • Table A: The Table provides are clearer distinction in the mechanisms of action, but an additional edit to the table would be helpful – having the first section with a subheading of anti-inflammatories for management of gout attacks, and the second section with a subheading of agents for lowering serum urate	We have made the changes to Table A and Table 1 as recommended.
TEP Reviewer #3	Introduction	Scope: • Key question 4b: it's unclear why a range of 5-7 were chosen when treatment guidelines specify a target of <6mg/dL	The Key Questions were developed with input from Key Informants as part of the Topic Refinement process and peer reviewed. The Key Questions specified it as a range.
TEP Reviewer #3	Introduction	Scope: • Key question 5a is inappropriate to ask at this stage, in my opinion. The majority of patients are either not treated or undertreated. The big educational piece here should focus on appropriate management with treatment is needed, not provide a message that treatment can be stopped given that the majority are inappropriately managed to begin with.	The Key Questions were developed with input from Key Informants as part of the Topic Refinement process and peer reviewed.
TEP Reviewer #3	Introduction	Analytic Frameworks: • I would STRONGLY discourage the use of the term 'chronic gout'. These should be considered as two arms of the management strategy from the first instance that an individual is diagnosed as having gout. The two frameworks should be Treatment of Gout Attacks, and Treatment of Hyperuricemia in Gout. The reasoning behind my concerns about the use of the term 'chronic gout' is that it may be misconstrued to suggest that ULT is only needed at the stage of 'chronic' gout.	The term "chronic gout" was set originally at the time of Topic Nomination, was vetted by Key Informants during the Topic Refinement process, was vetted again during the public posting of the protocol, and cannot be changed now. Furthermore the term "chronic gout" is used in the literature (for example, in the 2014 Cochrane review co-authored by Rachelle Buchbinder, Claire Bombardier, and other noted rheumatologists).

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TEP Reviewer #3	Introduction	Findings: • ES-10, Line 31: It is unclear why low-dose colchicine was found to only have moderate strength of evidence. The RCT conducted to address this question was of much higher quality than all other prior colchicine studies.	In the evidence report we stated that "low dose colchicine is as effective as higher dose for reducing pain, with fewer side effects" and judged this as moderate strength evidence based on the one RCT, with between 52 and 74 patients randomized to one of the three treatment arms. We would not normally consider this to be a "large" trial, and since there is only one such study we judged this as moderate strength evidence.
TEP Reviewer #3	Introduction	Findings: • ES-10, Line 40: It is surprising that ACTH was found to have high strength of evidence given that the studies to date have been of low quality with high risk of bias, with inappropriate comparator arms often. (more details about this are written below in relation to the full report)	This is explained in the report: ACTH acts to increase the body's production of steroids. We judged steroids to be high SoE. However, as the two equivalence trials for ACTH were both judged to be at high risk of bias and steroids had three low risk of bias equivalence trials, we downgraded the ACTH SoE to moderate.
TEP Reviewer #3	Introduction	Findings: • ES-11, line 32: the vitamin C data for the one trial that was conducted among patients with gout actually demonstrated no effect of vitamin C (Stamp, et al. A&R. 2013, cited later in this review). The studies that have demonstrated an effect of vitamin C on serum urate were conducted among patients without gout. Those studies should not be translated to patients with gout since there could be differences in renal handling	We did not include the studies of patients without a diagnosis of gout. We now discuss the studies of nutritional factors in the risk for gout in the introduction as background studies. However one RCT assessed the role of vitamin C: we include that study in our review of original studies, so the finding is mentioned in the summary of key findings in the executive summary and in the report.
TEP Reviewer #3	Introduction	Findings: • ES-11: What about findings regarding dietary factors and risk of gout attacks? Lines 34-49 refer to serum urate, but there are studies that have evaluated risk of gout attacks, which is not mentioned here.	We have included the studies to which the reviewer is referring.

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TEP Reviewer #3	Introduction	Findings: • ES-12, line 13: this comment should be modified to acknowledge that the reason is the expected increase in flares with ULT initiation, particularly when prophylaxis is not appropriately used. Indeed, in the CONFIRMS trial, which is cited in this report, there was no spike in flares b/c prophylaxis was used in the first 6 months.	We do not feel this modification is necessary or appropriate since the available placebo-controlled RCT evidence has shown no differences between groups. The reviewer hypothesizes that this is due to the increase in flares with ULT initiation, and that these can be prevented with more prolonged prophylaxis. But this has not been proven, and an equally testable hypothesis is that prolonged use of prophylactic levels of colchicine or NSAIDs is reducing the gout flare rate, and not the ULT at all.
TEP Reviewer #3	Introduction	Findings: • ES-13, line 5: It is unclear why the authors found insufficient evidence regarding monitoring serum urate	We agree that if the reviewer accepts that treating to a specific target is appropriate therapy, then monitoring serum urate should be rated higher than "insufficient". However, as we judged the SoE for a treat to target strategy to be "Low", without a hypothesis testing study supporting monitoring we could not judge the SoE for monitoring as anything other than insufficient.

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TEP Reviewer #3	Introduction	Findings: • ES-13, line 6: it is unclear why the authors found low SoE regarding treat-to-target	We provided detailed explanation in the report. A treat-to-target approach would require RCT level evidence of that strategy in order to be considered high strength evidence. Diabetes, hypertension, and hyperlipidemia all also had strong observational evidence supporting associations with various adverse outcomes, had RCT evidence showing that lowering A1C, blood pressure, and LDL resulted in improved outcomes, all had one-size-fits-all treat-to-target management strategies advocated by respected professional societies, and all three treat-to-target strategies, when actually tested in RCTs, were found to produce less benefit and more harm than predicted. Therefore, we judge that, in gout, a treat-to-target strategy will require RCT level of evidence for support before this EPC can rate it as strong evidence.
TEP Reviewer #3	Introduction	Findings: • ES-13, line 30: these observational studies did demonstrate recurrence of gout attacks a few years after being off therapy; the median time to recurrence of gout in one of Perez-Ruiz's studies (which is not in the reference list in this document, but should be included for a full picture: DOI 10.1002/art.22232) was 47 months for patients who had a lower SUA at time of ULT withdrawal, and 49 months for patients who had a lower SUA during treatment; it was less than 3 years (34 mo) for patients with higher SUA levels. In the paper cited, the median time to recurrence overall was 47-mo. Thus, this finding should be modified because it inappropriately states that they did not have an increased risk of acute gout attacks; these patients DID have recurrent gout at a median of 3-4 yrs post-discontinuation. (These two papers are not independent as there is an overlap in the sample). Given that this is a chronic disease, it is unfortunate to be giving PCPs the thought that withdrawal may be ok when the vast majority are under-treating (if they are treating at all!)	We have added the additional Perez-Ruiz study to the text in the final report under "Discontinuation of urate lowering therapy" where the other Perez-Ruiz is discussed.
TEP Reviewer #3	Introduction	Findings: • Why wasn't ice commented upon since it was evaluated later in the full report?	We have deleted "ice" as a separate intervention since it was not included in the PICOTs and Key Questions.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Introduction	Discussion: • ES-14: It seems contradictory to state that strong conclusions were reached about the usefulness of anti-inflammatory drugs since symptoms are due to inflammation related to urate crystals, which occur when serum urate rises above saturation; yet, the SoE is deemed to be low for the utility of lowering serum urate below a particular threshold.	As explained in the report, a treat-to-target approach would require RCT level evidence of that strategy in order to be considered high strength evidence. Diabetes, hypertension, and hyperlipidemia all also had strong observational evidence supporting associations with various adverse outcomes, had RCT evidence showing that lowering A1C, blood pressure, and LDL resulted in improved outcomes, all had one-size-fits-all treat-to-target management strategies advocated by respected professional societies, and all three treat-to-target strategies, when actually tested in RCTs, were found to produce less benefit and more harm than predicted. Therefore, we judge that, in gout, a treat-to-target strategy will require RCT level of evidence for support before this EPC can rate it as strong evidence.
TEP Reviewer #3	Introduction	Discussion: • ES-14, line 16: 'uric acid crystals' should be changed to 'urate crystals'	We have made this change
TEP Reviewer #3	Introduction	Discussion:• ES-14, line 17: 'serum rate' should be changed to 'serum urate'	We have made this change
TEP Reviewer #3	Introduction	Discussion: • ES-14, line 53: I think it's inaccurate to state that tophi are rarely seen in primary care; PCPs may not be carefully looking for tophi, which can often be small and require careful palpation to identify them, or may only be radiographically evident, but nonetheless, radiographically evident tophi are already causing joint destruction.	The proportion of patients with tophi in the major ULT RCTs are 20% (APEX), 24% (FACT), and 20% (EXCEL), and 21% (CONFIRMS). Whereas the proportion of patients with tophi in the Janssen trial, which explicitly came from primary care was 10%. Furthermore, population based estimates of the proportion of primary care patients with gout who have tophi are as low as 0.5% (246 of 52,164 patients).(PMID: 25536262) Whether this is due to detection bias is a testable question, but we can't assume it.

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TEP Reviewer #3	Introduction	Discussion: • ES-15, line 25: There are studies that have reported reduction in flares after one year, but these tend to be long-term extension studies, often open-label.	We have added the term "randomized controlled".
TEP Reviewer #3	Introduction	Discussion: • ES-15, line 37: The interpretation of this study's results are a bit liberal. As I indicated above, the patients in this cohort (which has had 2 publications on this topic, not just the one reported here) had recurrent gout attacks within 3-4 yrs of ULT discontinuation. This message to PCPs that ULT can be discontinued is misleading and should be greatly tempered.	We have now included this study in our review. Our review reports the evidence, it is up to other groups to interpret this evidence into a message for PCPs.
TEP Reviewer #3	Introduction	Discussion: • ES-16, line 9: The message regarding ULT initiation being a risk factor for gout flare needs to be modified to remind the reader that this increased risk is only present within the first few months of initiation due to well-understood biology, and that prophylaxis can markedly reduce this risk, which is why prophylaxis is recommended. As mentioned above, in CONFIRMS, there was no spike in flares b/c prophylaxis was used for the 1st 6 months. Without acknowledging this important role of prophylaxis, these statements send an incomplete message to PCPs.	We have modified this sentence to indicate that what remains to be demonstrated is the balance between long term benefits and harms.
TEP Reviewer #3	Introduction	Discussion: • Table B: It is unclear why ACTH is given a 'high' SoE when the trials have been of low quality and high risk of bias?	We provided an explanation in the body of the report. ACTH acts to increase the body's production of steroids. We judged steroids to be high SoE. However, as the two equivalence trials for ACTH were both judged to be at high risk of bias and steroids had three low risk of bias equivalence trials, we downgraded the ACTH SoE to moderate for the final report.
TEP Reviewer #3	Introduction	Discussion: • Table B: The systematic review of vitamin C is not directly relevant to patients with gout. The one RCT that was done in gout patients (by Stamp, et al. A&R 2013) is not cited/reviewed here in this table, although it was reviewed elsewhere in the full report – why?	We have removed the SR from the table. We have now considered the Stamp study in Table B.
TEP Reviewer #3	Introduction	Discussion: • Table B: Again, I would STRONGLY caution against giving only "half" the story regarding discontinuing ULT given that the median time to recurrence of gout attacks was 3-4 yrs in both publications (only one of which is cited here).	We have added the additional Perez-Ruiz study to the text in the final report under "Discontinuation of urate lowering therapy" where the other Perez-Ruiz is discussed.
TEP Reviewer #5	Introduction	The background section is excellent. Please see general comment regarding other parts of the introduction section.	No response necessary

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Methods	Methods are appropriate. Commend the authors for their strength of evidence ratings for acute gout. GRADE purists sometimes demand many placebo controlled trials before reaching an SOE of moderate to high. The authors used Bayesian good sense taking into account the priors for these medications. However, not all systematic reviewers do this, and the authors may want to spend more space in the full report justifying the use of sometimes indirect evidence and strong biologic rationale in the assessment of SOE.	We have explained our approach and added an example in the Methods section to explain how we assessed the SoE.
TEP Reviewer #1	Methods	yes	No response necessary
Peer Reviewer #2	Methods	Page 38, first par: Please spell out acronym DASH diet (if it is an acronym)	We have spelled out DASH in the report
Peer Reviewer #2	Methods	Page 38, pharmacologic agents: Were intramuscular anti-inflammatories considered? If not, why not as these can be usually administered in a primary care setting.	The mode of administration of NSAID was not an inclusion/exclusion criterion. We did not identify any eligible studies of intramuscular NSAIDs.
Peer Reviewer #2	Methods	Page 38-9: How were the outcomes selected? Were the OMERACT domains for acute and chronic gout considered (Schumacher et al, J Rheumatol 2009)?	These outcomes were selected by an open process involving public, various stakeholder groups including PCPs, gout specialists and the AHRQ representatives. The OMERACT domains were not explicitly considered independent of the above process.
Peer Reviewer #2	Methods	Page 38-9: Acute gout outcomes Also, I am confused about the short term and the long term outcomes for acute gout treatment. How long is longer-term outcomes for acute gout treatment? If it is months, then I wonder if these are relevant outcomes, as the aim in acute gout is to relieve a flare that, even if untreated will last less than two weeks. For example, it is not expected that it will have any impact in SUA. Also, in acute gout, treatment is usually given for a short time (less than 2 weeks). Regarding the safety outcomes, were only these specific outcomes selected? No number of AE, or of Serious AE?	Short term outcomes were defined as a matter of days. Long term outcomes were defined as greater than one month. These decisions were made at the protocol stage and involved input from the public, various stakeholder groups including PCPs, gout specialists and the AHRQ representatives. We did not find any studies of acute gout that reported long term outcomes. For AEs we did look for any AEs not just those listed.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Methods	Page 39, diet outcomes: Why were the selected outcomes different from the acute gout treatment of chronic gout treatment? The bottom line, is that the aim of treatment is the same irrespective of whether it is pharmacologic or non-pharmacologic, so perhaps the outcomes selected a priori should be the same.	We considered any dietary studies on gout treatments regardless of the outcomes and we have reworded that section accordingly
Peer Reviewer #2	Methods	Page 39: timing: What does this timing mean? For example, in acute gout, is this the time where the short-term outcomes are measured? How about the long-term outcomes above?	Short term outcomes were defined as a matter of days. Long term outcomes were defined as greater than one month. These decisions were made at the protocol stage and involved input from the public, various stakeholder groups including PCPs, gout specialists and the AHRQ representatives. We did not find any studies of acute gout that reported long term outcomes. For AEs we did look for any AEs not just those listed.
Peer Reviewer #2	Methods	Page 40, first par: The rationale for including only papers from 2010 onwards should be discussed somewhere. For questions with recent SLRs (most questions) it seems to work fairly well. I wonder however if some studies are not missed in those questions with no retrieved SLRs.	This is a commonly used strategy in topics that have already been the subject of numerous prior systematic reviews, e.g. don't reinvent the wheel". We established that there were SRs covering every KQ except #5 using existing systematic reviews, reference mining, and input from experts resulted in 74 included articles published prior to 2010, so it is not as if we did not find or include older studies.
Peer Reviewer #2	Methods	Page 40, first par: the method used for selecting the studies is confusing. Was there no language restriction or did studies need a) an English abstract and b) to be written in Chinese, French, ...	We have revised this sentence
Peer Reviewer #2	Methods	Page 40, first par: in the results section you talk about papers retreived from hand searching (as different from reference mining). Please specify in the methods what were these hand searches.	We have removed "hand searching" from the flow as this was a typo.
Peer Reviewer #2	Methods	Page 40, first par: also what was the policy for conference abstracts for which there was no full-length report/paper? From the results, I gather they were excluded. This should be stated in the methods.	This was a typo as we included conference proceedings/abstracts.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Methods	Methodologically, the approach appears to be quite sound. A few specific comments: 1. Realizing this likely follows a "template" it would be helpful for the reader to be provided more information on SoE definitions (e.g. low, medium, high, and insufficient), perhaps with examples of what is needed to attain these different levels. While references are provided, it would be preferable not to have to refer to the source documents for these definitions, as this is a crucial enough issue.	We have added the official GRADE text definition of low, moderate, high, etc. But since it is not a formula, we can't provide text about the kinds of evidence needed to achieve this. We did provide a detailed explanation of the evidence used to reach each SoE criteria.
TEP Reviewer #2	Methods	2. Additional detail regarding PICOT question development would be helpful. How were these questions initially identified? Who vetted these questions? The literature is replete with poor quality in gout care and "under-treatment" is a recurring theme in this literature, yet one of the major questions here was whether effective and safe ULT could be discontinued. Given limited resources, I suspect this would not have been a priority question for most gout experts. That does not diminish the potential importance of this question in the primary care arena but additional context referent to question development would be highly informative.	We developed key questions, PICOTS and the review protocol, using an open process involving public, various stakeholder groups including PCPs, gout specialists and the AHRQ representatives In the ES and in the Methods, the report explains the details how these Key Questions and PICOTS were developed. In addition AHRQ methods guide also provide more detailed information and it is available online. KQ5 was an item of interest to the American College of Physicians.
Peer Reviewer #3	Methods	yes to all of the above	Thank you
TEP Reviewer #3	Methods	These are appropriate.	Thank you
TEP Reviewer #4	Methods	Limiting this section on Nutrition to RCTs was challenging. If there are no suitable RCTs then it is logical to exopand the search and include observational studies that explore relationship between these foods just prior to gout attacks such as in the Zhang studies. The logic of expanding the types of studies to including these studies that might address the components of the diet is not explicit in the nutrition section of the report.	After considering your points, we decided that because the report focuses on management of gout, we should not include studies on nutritional risk factors for developing gout in our review of original studies. Therefore, we now review the evidence for a role of diet in risk for gout or high serum urate in our introduction. The Results chapter now includes only studies of the effects of diet on management in peoples already diagnosed with gout, since the report focuses on gout management.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	Methods	Nutrition Therapy/Dietary section The systematic review methodology and results appear to be much clearer for the sections that address medication therapy than those that address Question 2 – Dietary and lifestyle management. The nutrition therapy section is under-developed and not well explained. The tables are incomplete and lack sufficient detail to be useful. For example in the medication tables the evidence is summarized with dose and reported outcomes. While there appears to be very limited research, even the research that is available is inadequately described. Despite including the column headings, the report does not include the description of the participants/ number of subjects, the dose of the intervention, and the exact reported outcomes.For example from reading Table 7 it is impossible to understand the content of the MOI systematic review. I believe the actual interventions are 3 different skim milk interventions and the % reduction was reported in the article, but not in the table. Another example, the reader also doesn't know that the Zhang study had 633 participants diagnosed with gout. In some cases the text includes some of the details, but they should also appear in the table to be accurate and complete.	We revised the Results on diet and management of gout. We decided that because the report focuses on management of gout, we should not include studies on nutritional risk factors for developing gout in our review of original studies. Therefore, we now review the evidence for a role of diet in risk for gout or high serum urate in our introduction. The Results chapter now includes only studies of the effects of diet on management in individuals already diagnosed with gout, since this report is focused on management of gout. Along with that, we revised Table 7, omitting studies on persons not diagnosed with gout and adding the study level details and findings shown in the tables for pharmacologic treatments.
TEP Reviewer #5	Methods	Please see general comments. Also, for what it's worth, I find PICOTs to be generally off-putting. It has the effect of giving equal weight to things that are not equally important, and I'm not sure that a non-SR crowd completely knows what to make of it (e.g. are these completely finalized a priori, or are they based upon what you found along the way?) A couple of sentences of explanation might help a little bit.	PICO or PICOTS are commonly used in EBM and are required to use for SRs.
Peer Reviewer #1	Results	While the results in general confirm current recommendations, I think many providers are still prescribing relatively high doses of colchicine for acute gout. The comparison of colchicine to other acute treatments could be emphasized more given the recent marked increase in the price of colchicine. Some discussion regarding use of this medication in individuals with renal impairment would be helpful.	We have modified the text on use in renal impairment. Unfortunately, there are no comparative effectiveness trials of colchicine compared to other acute gout treatments. Price is not considered in this report.
Peer Reviewer #1	Results	ES-17: Dietary therapy advice seems to be based on one small study with only 30 subjects. With just one trial, should this be 'indeterminate' or 'insufficient' SOE, rather than 'low'? On page 46 of the main report the SOE is described as insufficient.	We agree and have changed this to insufficient
Peer Reviewer #1	Results	Page 18: I like the table of the 'coverage' of systematic reviews for trials. Is the limited consistency due to different goals of the trials, different inclusion criteria, or just lack of consistency?	Mostly this is different goals. Reviews by Khanna, van Durme, and Wechalekar are meant to be comprehensive, while the other reviews were usually drug-specific.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	Page 19: Please tell the readers the range of dosing for 'high dose' and 'low dose' colchicine. We aren't told that until the harms section several pages later.	This was added
Peer Reviewer #1	Results	Page 70: What is the significance of HLA status for this paper? I had to look it up.	This explanation was added to the PICOTs.
TEP Reviewer #1	Results	detail is appropriate	Thank you
Peer Reviewer #2	Results	Page 44, last par: Do the seven observational studies on dietary risk factors fulfil the inclusion criteria? According to the methods "For studies of efficacy and effectiveness, we included only randomized controlled trials. Observational studies were included for the assessment of rare adverse events." If they do not fulfill the inclusion criteria they should be excluded. Please check that all other included papers fulfill the inclusion criteria as well.	We have omitted the descriptions of the observational studies that didn't enroll gout patients. However, because we did include a small number of important cohort studies on gout patients, we have modified our description of our inclusion criteria slightly.
Peer Reviewer #2	Results	Page 44, last par: one non-published abstract was included. However, others were excluded for "conference proceedings/presentations/ abstracts. Please clarify how these were excluded and the remaining one was included.	This was a typo. We did include conference abstracts and have revised the text.
Peer Reviewer #2	Results	Page 49, table 2: Was Tumrasvin 1985 included in any of the SLRs?	We have marked that it was included in the Wechalekar, 2014 review
Peer Reviewer #2	Results	Page 50, par 1: If I understand this correctly, first you are looking only at studies vs placebo and then you look at comparative efficacy between treatment. Perhaps, this should be made clear in the title of the sections and something like "placebo controlled" or similar should be added initially as a counterpoint to "comparative efficacy" further on. For easiness to read.	We have added this
Peer Reviewer #2	Results	Page 52, par 5: Please double-check the aim of the study by Taylor et al. I believe that Taylor investigated whether initiating allopurinol early did not harm (i.e. prolong the gout flare) the patients with an acute flare.	We rephrased the sentence.
Peer Reviewer #2	Results	Page 52: What does stratification per acute episode in the context of studies evaluating treatment for acute gout mean?	We rephrased this--we meant to say duration of the acute episode
Peer Reviewer #2	Results	Page 52: Were all included patients in the Karimzadeh study presenting with an acute gout episode? the outcome you are presenting here pertains to the KQ3 (flare prophylaxis).	That is correct. The text refers readers to KQ3 for a discussion of the Karimzadeh study.
Peer Reviewer #2	Results	Page 54, strength of evidence: NSAIDs, glucocorticoids and ACTH for acute gout have all been given a high strength of evidence. However, this is based not in the evidence per se, but rather on the biologic plausibility and the extrapolation from other disorders. However, there is a lack of high quality trials, especially for ACTH where there is a single RCT wth a 75% completer rate. I would consider downgrading the evidence to moderate.	We agree. We downgraded the strength of evidence to moderate.

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Peer Reviewer #2	Results	Page 74, last par: The sentence states "On the other hand, results from a meta-analysis by Zhou et al 201380 found that once gout had progressed to the acute arthritis stage...". However, what is the stage before the acute arthritis stage? Asympotmatic hyperuricemia?	The authors were referring to studies of patients experiencing an acute gout flare. We have revised the wording.
Peer Reviewer #2	Results	Page 78, table 8: Please revise the title as it also includes non-pharmacologic therapy (acupuncture).	We have revised the content and title of the table
Peer Reviewer #2	Results	Page 87, 2nd par: Please check this first sentence: "The only new eligible study we identified reports was published as an abstract only."	We have revised the sentence
Peer Reviewer #2	Results	Page 87, 3 par: This presents the results of a study that is only in abstract form. Please include how abstracts/conference proceedings were handled in the methods section.	This was a typo in the methods section. We did include abstracts/conference proceedings.
Peer Reviewer #2	Results	Page 102, par 2: The sentence "Compared to patients with normal renal function, patients taking either febuxostat or allopurinol with mild renal impairment achieved higher rates of target serum urate" is confusing. I would read this that patients with mild renal impairment were more likely to achieve a SUA <6mg/dL (target).	We have revised this text
Peer Reviewer #2	Results	Page 113, last par: Should the strength of evidence be judged as low, or as insufficient? Being low, seems to suggest that there is some evidence to support it.	We have downgraded the strength of evidence to "insufficient".
Peer Reviewer #2	Results	Page 114: With this strategy you examine the relationship between measuring sUA and adherence. However, the initial question (KQ4a) and the statement in the Key Points is much broader as it talks about the relationship between monitoring SUA and outcomes. In this manner, I would argue that if the outcomes of patient who achieve target SUA (i.e. <6mg/dL) are better than outcomes of patients who do not achieve target SUA, then monitoring can be associated with improved treatment outcomes (because that is the only way to know if you have achieved target SUA and thereby titrate the dose of ULT). I can see that this is dealt with in KQ4b, but this is relevant to KQ4a too. I think that a short statement in Strength of evidence is insufficient as this a clinically very relevant point.	We agree with this rationale, but it requires experimental evidence supporting a treat-to-target strategy, which does not exist. Therefore, we can't agree that an indirect argument favoring monitoring has a strength of evidence, and judged it as insufficient.
TEP Reviewer #2	Results	I believe the level of detail and study characteristics are quite clearly provided and adequate for the audience. This are aided by well crafted tables. I am not aware of any RCTs or SRs missed in the report.	Thank you
Peer Reviewer #3	Results	see above in general comments	No response necessary

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Results	Some of the details of the results need further clarification or modification, as outlined in my comments below. Some of the key messages would benefit from some modification, as outlined in my comments below. Some studies that would be worth commenting upon or including are also included in my comments below.	Responses are given to the specific comments.
TEP Reviewer #3	Results	Full Report: • Page 2 (page 33 of 176): same comments as above re: “Chronic gout” terminology, and about moving ‘management’ into its own subsection so as not to imply that the management being discussed is only for the ‘chronic’ stage of gout.	The term "chronic gout" was set originally at the time of Topic Nomination, was vetted by Key Informants during the Topic Refinement process, was vetted again during the public posting of the protocol, and cannot be changed now. Furthermore the term "chronic gout" is used in the literature (for example, in the 2014 Cochrane review co-authored by Rachelle Buchbinder, Claire Bombardier, and other noted rheumatologists).
TEP Reviewer #3	Results	Full Report:• Page 34 of 176: IL-1B antagonists should not be discussed under management of hyperuricemia; they should be discussed under management of gout attacks.	We added that they do not work by lowering serum urate levels
TEP Reviewer #3	Results	Full Report:• Page 38 of 176, line 13 or line 37: why was ice not considered as an ‘alternative’ or ‘co-intervention’?	We have deleted "ice" as a separate intervention since it was not included in the PICOTs and Key Questions.
TEP Reviewer #3	Results	Full Report:• Page 50 of 176: ice was assessed, but not reported in the ES – why?	We have deleted "ice" as a separate intervention since it was not included in the PICOTs and Key Questions.
TEP Reviewer #3	Results	Full Report:• Page 53 or 176: risk of CHF with NSAIDs should also be mentioned. The issue of CVD should probably be revisited given the recent labeling change for OTC NSAIDs by the FDA. For corticosteroids, the issue of fluid retention is particularly important for CHF; dexamethasone is preferred in those cases.	We have added this to the list of rare AEs from NSAIDs

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Results	Full Report:• Page 54 of 176: The purported effects of ACTH in gout are not just via cortisol release, but rather through unique effects on melanocortin type 3 receptor, which is thought to have effects on MSU-induced neutrophil migration, independent of HPA-axis stimulation (i.e., independent of corticosterone), and these effects are seen in adrenelectomized rats (i.e., again, independent of cortisol). Thus, making an assumption that the effects and harms should be similar to glucocorticoids is not appropriate.	The report already indicates that the mechanism of action is only in part due to cortisol production. The report notes that in the only two studies in gout patients, no side effects were reported. Furthermore, according to secondary sources, the side effects of ACTH treatment, in other conditions are essentially identical to steroid treatment, e.g.,: Cushing's syndrome; Easily angered or annoyed; Excessive hairiness; Scaly oily skin problem; Skin discoloration; etc. We feel justified in the report saying the expected harms are "probably" very similar to use of glucocorticoids.
TEP Reviewer #3	Results	Full Report:• Page 72-73 of 176: additional observational data regarding alcohol is available beyond simply risk of incident gout. There is a study that evaluated alcohol intake with risk of triggering gout attacks (AJM 2006 and 2014).	This study has now been added to the text on this section.
TEP Reviewer #3	Results	Full Report:• Page 73 of 176, line 34: The systematic review of vitamin C only included subjects without gout. The Stamp RCT, which is cited here, evaluated the effect of vitamin C among patients without gout did not demonstrate an effect. Renal handling among patients with gout is different from those without gout; findings among subjects without gout should not be extrapolated to patients with gout.	We have removed the SR from the table. We have now considered the Stamp study in Table B and Table 20.
TEP Reviewer #3	Results	Full Report:• Page 77 of 176, line 12: in light of the preceding comment, why is the Stamp trial not cited here, and why is the SoE for vitamin C low when the relevant RCT showed no benefit and the systematic review is of likely low relevance to patients with gout? Would this not warrant insufficient?	We have rated the findings regarding individual nutrients as having insufficient evidence.
TEP Reviewer #3	Results	Full Report:• Page 86 of 176: Harms of febuxostat should cite the similar prevalence of skin rash in these trials as there is from allopurinol since PCPs may not be aware that it is similar.	We have added that skin rash is also seen with febuxostat
TEP Reviewer #3	Results	Full Report:• Page 113 of 176, line 55: I don't think it's accurate to state that there are no RCTs that have examined gout flare beyond 6 months; many of the febuxostat studies have had longer-term follow-up, but those phases were not blinded.	We have modified this to indicate there are no blinded placebo controlled trials of ULT reporting gout flares beyond 6 months.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Results	Full Report:• Page 115 of 176, line 17: I think this conclusion is problematic. Without monitoring of serum urate, ULT dose cannot be adjusted. Without dose adjustment, over half of patients remain inadequately treated with serum urate levels that remain in the hyperuricemic range, putting them at risk for recurrent flares and ongoing urate deposition that leads to tophi, joint destruction, and functional limitations.	Our evidence report does not conclude that monitoring does not improve outcomes. Rather we found no evidence that monitoring improves outcomes and the only evidence about adherence did not support a positive association. However, we have acknowledged that monitoring is the only way to determine if ULT is having an effect on SUA and have added this to the summary.
TEP Reviewer #3	Results	Full Report:• Page 115 of 165, line 31: The threshold is 'absolute' based on basic chemistry properties of urate; what is not 'absolute' is the clinical effects because serum urate is not a perfect measure of total body urate burden. Thus, some patients whose serum urate is below this threshold may still flare b/c of their tophaceous burden which isn't perfectly reflected in the serum urate levels. Further, while a patient may be apparently 'clinically asymptomatic', they continue to have urate deposition if they remain hyperuricemic. We have seen far too many patients who may be deemed to be 'asymptomatic' because they are not having flares any longer, but their tophi continue to grow, leading to joint destruction and functional limitations. Further, the mean serum urate level in US adults is 5.48 mg/dL, so the treatment target being recommended is actually simply getting patients to the mean level already seen in US adults.	We deleted this phrase
TEP Reviewer #3	Results	Full Report: • Page 115 of 176, line 44: It is perplexing that the authors don't appear to support a treat-to-target threshold, yet cite data from analyses combining trial data of 1800 subjects that demonstrate lower attacks with SUA was <6mg/dL compared with those whose SUA was >=6mg/dL	The difference here is that the 1800 subjects were ones who achieved an SUA below 6 based on whatever was the treatment given then by their doctors. As shown in trials of treat-to-target in diabetic lipids and hypertension, when it becomes an expectation that all patients be given increasing doses of medication to reach this target is where the trouble begins.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Results	Full Report:• Page 116 of 176, line 18: There have been a few studies that have evaluated the effect of hyperuricemia on renal disease, and of intervening upon hyperuricemia demonstrating renal benefits. Some of these have been communicated via email.	We can't use the results of the listed studies as evidence for reducing the risk of renal disease for the following reasons: first, the main outcome is a lab value rather than a clinical sign or symptom that can be directly felt by the patient, and second, the size of the effect, if the results of the Whelton studies are taken at face value, is nowhere near the size of the effect of ULT on the risk of acute gout flare. Whelton and colleague's two studies conclude that a 1 mg/dL increase in sUA is causally related to a 1 ml/min/1.73m 2 per year change in GFR. In other words, if a 45 year old male with gout who had an achieved sUA of 7.0 on ULT was placed on a TTT strategy and had treatment intensified to achieve an sUA of 6.0, and he maintained this for 30 years, then by age 75 he would have had 30 ml/min/1.73m2 better GFR than if he hadn't. What the clinical effect of this is, in terms of CKD or dialysis, for those men surviving to age 75, is not clear. For some 75 year old men, this is probably equivalent to a pretty big difference in clinical outcome. For others, it probably is not. And then one has to consider what kind of AEs might occur as a result of trying to achieve and maintain a sUA of 6.0 for 30 years. We are not saying that the benefits exceeding the risks of such a strategy is not a plausible outcome, but as far as there being evidence to conclude that treating "asymptomatic" sUA reduces the risk of clinical renal outcomes, this is not there yet.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Results	Full Report:• Page 116 of 176, line 34: treating to target for serum urate does not increase risk of side effects once a patient has already passed the first 6-month period (Stamp, et al. A&R, 2012). Further, it seems that the authors have not considered that the mean serum urate levels in US adults is actually <6mg/dL (according to NHANES data). Thus, the treat-to-target level of 6 is not excessive in comparison with the average US adult; one also must bear in mind that that mean level is actually lower if one were to remove the gout patients out of the sample. As well, unlike treating blood pressure (too low can cause side effects) or blood sugar (too low can cause side effects), there are no side effects to having a serum urate of 5mg/dL, for example. The lower the serum urate, in fact, the faster the urate clearance and tophus dissolution. Thus, this sentence should be rephrased or modified to acknowledge that the there is no evidence to suggest an alteration in benefit:risk ratio, unlike for management of hypertension or diabetes.	We now include a discussion of the results of the Stamp and colleagues. However, the concern about lowering SUA to less than 6 is not the physiologic effects on the body but rather the increased risk of side effects, monitoring, and time associated with intensified treatment. However, the evidence about lower levels altering the risk benefit ratio for diabetes and hypertension come from RCTs of TTT strategies.
TEP Reviewer #3	Results	Full Report:• Page 116 of 176, line 47: it is difficult to reconcile the low SoE, though I understand that the authors are taking issue with a specific threshold not having been formally tested in a RCT. Nonetheless, the concerns from diabetes and hypertension about lowering targets too low is not directly translatable to the lowering of serum urate, particularly with the levels that we are talking about. Please remember that the mean serum urate levels in US adults is 5.48mg/dL (6mg/dL for men and 4.87 mg/dL among women) based on NHANES data. Thus, targeting a serum urate level of 6 is in keeping with the mean levels of the US adult population.	As explained in the draft report, a treat-to-target approach would require RCT level evidence of that strategy to be considered high strength evidence. Diabetes, hypertension, and hyperlipidemia all also had strong observational evidence supporting associations with various adverse outcomes, had RCT evidence showing that lowering A1C, blood pressure, and LDL resulted in improved outcomes, all had one-size-fits-all treat-to-target management strategies advocated by respected professional societies, and all three treat-to-target strategies, when actually tested in RCTs, were found to produce less benefit and more harm than predicted. Therefore, we judge that, in gout, a treat-to-target strategy will require RCT level of evidence for support before this EPC can rate it as strong evidence. The concern about lowering SUA to less than 6 is not physiologic effects on the body but increased risk of side effects, monitoring, and time associated w/intensified treatment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Results	Full Report:• Page 117 of 176, line 24: as indicated above, the authors have only provided half the story from this study, and there are actually 2 papers emanating from this cohort study, both of which have demonstrated a median time to recurrence being 3-4 yrs (and even 2 yrs in a certain subset). Without providing these complete data, the information provided here is misleading.	We have added the additional Perez-Ruiz study to the text in the final report under "Discontinuation of urate lowering therapy" where the other Perez-Ruiz is discussed.
TEP Reviewer #3	Results	Full Report:• Page 117 of 176, line 56: this indicates that one-third of subjects had recurrent gout in about 1.5 yrs; it is not known how many would recur with longer follow-up. Again, this time off ULT among patients with gout means that there is ongoing urate deposition.	We added that the lack of recurrence was subject to the duration of observation.
TEP Reviewer #3	Results	Full Report:• Page 118 of 176, line 7: this is only one of the 2 relevant citations from this study related to this question. I don't think the authors have appropriately summarized the findings as median time to recurrence was 3-4 yrs.	We have added the additional Perez-Ruiz study to the text in the final report under "Discontinuation of urate lowering therapy" where the other Perez-Ruiz is discussed.
TEP Reviewer #3	Results	Full Report:• Page 118 of 176, line 52: Why is this low SoE instead of insufficient SoE?	We agree with this comment and have changed this to insufficient.
TEP Reviewer #3	Results	Full Report:• Page 119 of 176, line 4: why is SoE moderate when in other instances the authors made certain assumptions that led them to a 'high' SoE despite less data than is here for prophylaxis based on thinking about mechanisms.	We judged the placebo controlled RCT data about use of NSAID in other conditions, for example as proving substantial evidence for the likely effect of NSAIDs in acute gout. In the case of duration of prophylaxis, we are making cross-study observational comparison and could only reach a SoE of moderate in this situation.
TEP Reviewer #3	Results	Full Report:• Page 121 of 176, line 34: again, as above, this sentence needs to be modified because there was a median time to recurrence of 3-4 yrs.	This study has now been added to the text on this section.
TEP Reviewer #3	Results	Full Report:• Page 122 of 176, line 8: sentence can be modified to acknowledge that open-label extension studies have demonstrated a beneficial effect	We added that this placebo-controlled RCT

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Results	Full Report:• Table 20: I take issue with the high SoE for ACTH for reasons given above since it seems that the authors equated ACTH with glucocorticoid effects based on inaccurate assumptions about putative mechanism of action. I also take issue with the low SoE for vitamin C (would insufficient may be more appropriate given that the study among gout patients was not positive?). I also take issue with ULT discontinuation without the full details as outlined above, and take issue with the 'low' SoE (insufficient would seem to be more appropriate)	This is explained in the text: ACTH acts to increase the body's production of steroids. We judged steroids to be high SoE. However, as the two equivalence trials for ACTH were both judged to be at high risk of bias and steroids had three low risk of bias equivalence trials, we downgraded the ACTH SoE to moderate. We have changed the SoE for vitamin C and all individual nutrients to "insufficient". We changed the discontinuation SoE to insufficient.
TEP Reviewer #4	Results	3. Inadequate characterization of nutrition therapy From reading the report no one would understand what the components of nutrition therapy are that are being investigated. The report would benefit from identifying the common components that are thought to reduce serum urate levels either from dietary sources or from production at the beginning of the chapter while including adequate nutrients: Limit meat, poultry and fish (usually 4-6 ounces per day), avoid fried and fatty foods, eliminate high fructose corn syrup, increase fruits, vegetables and whole grains, limit alcohol, especially beer) and drink 8 glasses of water per day, restrict calories of overweight to lose weight. Figure A on Page ES-5 starts a description (Low Purine, Alcohol, hydration, but drops off with "etc"…. If this is the common nutrition therapy, then these would be the components you would expect to see identified in the research as part of the search strategy and the questions would be arranged around these topics. Your review identified other types of interventions, such as Cherry juice /extract, Vitamin C supplementation and enriched milk, however those are not mainstreat nutrition therapy. This section would be greatly improved if the studies were actually organized and characterized with regard to the components of dietary lifestyle changes that are routinely included and then in addition the more "novel" nutrition therapies.	We have revised the descriptions of the studies. We now discuss diet and gout risk in the introduction, in order of types of foods and nutrients, which provides the background for understanding the studies. We have also reorganized the table that provides study details and the descriptions of the nutrition management studies in the response to KQ2.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	Results	4. Choice of type of studies to include and quality of studies Given that there don't appear to actually be any RCTs that actually implement this dietary regime and actually MEASURE the fidelity of the intervention this would be characterized as no evidence, not evidence of ineffectiveness. The text references two RCTs that are not included in the table: 1) Holland and McGill and 2) Zhang 2012 on macronutrient intake. For the second one there is an inadequate description of the intervention in the text—I believe it is actually a comparison of protein and purine intake that should be further elaborated rather than characterizing it as macronutrient intake. If there are no suitable RCTs then it is logical to include observational studies that explore relationship between these foods just prior to gout attacks such as in the Zhang studies. The logic of expanding the types of studies to including these studies that might address the components of the diet is missing from the report. And some of the relevant studies are also missing from the table, some discussed in the text but not included in the table (The second Zahn study). From scanning the table the Singh systematic review of observational studies appears the closes tso even addressing the normal components of nutrition therapy. However in the table the Singh (2011) systematic review in 2011 doesn't describe what types of studies are included nor does it describe what types of results are reported.	We completely revised the table and have added the descriptions of the RCTs and case-crossover studies to both the text and table. We now note in the Methods that we have included appropriately designed observational (case-crossover) studies where no RCTs exist. We also agree that absence of evidence is not evidence of ineffectiveness and have reflected this observation in our strength of evidence grades. Finally, we excluded the systematic review by Singh as it deals with risk for gout and not management of gout.
TEP Reviewer #4	Results	5. Potential omissions and errors in Table 7 Page ES-8 indicates that you identified 11 systematic reviews, 3 RCTs not included in prior STs and 7 observational studies on dietary risk factors. However the Table 7 on page 45 has 6 systematic reviews, 2 RCTs, and 7 observational studies and the text discusses additional studies that are not included in the table (Holland and McGill, the second Zhang study). And the text indicates that Stamp was included in a systematic review, however it is reported separately as RCT in addtiion to being included in the systematic review. Another example, shown in the table as Zhang, 2013 (is actually published in 2012) and the participants should be "633 people diagnosed with gout" not "Hyperuricemia?" What is the dose of cherry juice or cherry extract that was recorded? Why doesn't the Outcomes column indicate that there was a 35% reduction in gout attack if used alone or 75% if combined with allopurinol? There is a second Zhang research publication from this same population that evaluated quintiles of purine intake from animal and plant sources with recurrence of acute gout attacks with trends of P.0001 and p.004 respectively. This is discused in the text but not included in the table. It isn't clear why you would include one of the papers and not the second one?? The row of data in the table for Singh 2011 does even have the number of studies included, certainly doesn't describe the doses and outcomes column is completely blank?	We have decided to omit the two systematic reviews of studies that were not on gout patients (they are n ow described in the introduction). We also omitted the two systematic reviews that included the RCT on fortified milk and vitamin C, as the reviews did not add anything to the knowledge obtained from the studies themselves. Finally we added (to both Table 7 and the text) descriptions of the 3 published articles that report the findings of the BU Online Gout study (Zhang, 2012 a and b and Neogi 2014) and we have added the finding regarding cherry juice and allopurinol.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	Results	6. Text describing studies needs improvement The Holland and McGill 2014 description fails to mention that the study participants were on Urate Lowering Therapy and that the diet was in addition to medication (of unknown quantity)….and that there was no real measure of whether the dietary advice was implemented, in fact patient self reports showed that of the 30 patients only 1 patient in weight reduction group reported making any changes and 7 in intensive intervention reported making any change. Since part of dietary advice for gout would include weight reduction, this is really a compariion of two interventions for gout, not a usual care and intervention, more of a "less intensive" and "more intensive" intervention. The result is comparison of two different levels of changes being asked. It also fails to report that the intervention was only TWO counseling session in 6 months. This modification for treatment of gout is quite complex and the dose of education may not have been sufficient to elicit significant implementation of the actual dietary intervention (as reflected by low self reports of implementation).	We have completely revised the description of he studies of dietary interventions to include details of the participants, intervention and control conditions, as well as adjunctive treatments.
TEP Reviewer #5	Results	Please see general comments.	No response necessary
Peer Reviewer #1	Discussion/ Conclusion	I don't know where the right place would be for this, but historically the discussion of the choice between probenecid and allopurinol would revolve around renal function etc. I don't know whether there was ever much empiric evidence to support those biologic rationales, but the authors should refer to those clinical rationales, even if its in a negative way. Readers may look for it.	We have added this information.
Peer Reviewer #1	Discussion/ Conclusion	Nice discussion of the applicability of the RCT's, thank you. Great insight regarding the high % of patients with tophi in the RCT's, much higher than is seen in primary care, at least in my experience.	Thank you
TEP Reviewer #1	Discussion/ Conclusion	the methodology is clear, but I wonder if all of the intended audience which includes PATIENTS will understand the nuances of recommendations. For example page 17, line 40 states: High strength of evidence supports animal-derived ACTH formulation to reduce pain in acute gout. The reader has to go to page 23 lines 47-50 to find out that this study has 'high risk of bias'.	This evidence report does not make recommendations. Regarding the presentation of results, the AHRQ format requires the Key Findings be listed first and the supporting documentation comes later. And we note that we have downgraded the recommendation to moderate SoE.
Peer Reviewer #2	Discussion/ Conclusion	Page 121, research gaps: "In fact, some data suggest that once gout has been quiescent for 5 years, urate lowering therapy might be discontinued (as long as serum urate levels remain acceptable, e.g., < 7mg/dL)". It is unclear what quiescent means in this sentence. Also, the study supports this only for patients that had prior good control of SUA during treatment (<7mg/dL).	We changed "quiescent" to "asymptomatic"

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Discussion/ Conclusion	Most of my pertinent comments / suggestions refer to both the results and conclusions and are summarized below: 1. The importance of explaining how SOE is defined is uncerscored by what currently appears to be somewhat arbitrary assignments. Specifically, there is "strong" evidence supporting acute gout flare treatments in the absence of conclusive and sufficiently robust placebo-controlled RCTs. Juxtaposed to this is the assignment of a "low" level of evidence supporting a SUA treatment threshold (with < 6.0 mg/dl being the most commonly advocated treatment goal in gout). The report correctly states (p. 21) "symptoms are due to an inflammatory reaction to the deposition of urate crystals, which occurs when serum urate rises above its saturation point in the blood." This saturation point is well defined and thus it would follow based on the criteria proposed by AB Hill for causality (Reference 23 in this report) that there is overwhelming biochemical evidence that improving signs and symptoms in gout is dependent on lowering and maintaining serum urate concentrations to at least below this well defined threshold (< 6.8 mg/dl). This is further bolstered by the inflection points associated with this level seen in observational studies referenced in the report (Bhole V et al, Shoji et al, etc.). Admittedly, the data for lower thresholds advocated in guidelines (< 5 or 6 mg/dl) is lacking or low. The detailed discussion of this provided on page 115 would suggest more than a "low" level of evidence.	As explained in the draft report, a treat-to-target approach would require RCT level evidence of that strategy in order to be considered high strength evidence. Diabetes, hypertension, and hyperlipidemia all also had strong observational evidence supporting associations with various adverse outcomes, had RCT evidence showing that lowering A1C, blood pressure, and LDL resulted in improved outcomes, all had one-size-fits-all treat-to-target management strategies advocated by respected professional societies, and all three treat-to-target strategies, when actually tested in RCTs, were found to produce less benefit and more harm than predicted. Therefore, we judge that, in gout, a treat-to-target strategy will require RCT level of evidence for support before this EPC can rate it as strong evidence. The concern about lowering SUA to less than 6 is not the physiologic effects on the body but rather the increased risk of side effects, monitoring, and time associated with intensified treatment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Discussion/ Conclusion	2. The review appropriately notes limitations in terms of "applicability", siting that 10-25% of gout patients in RCTs have tophi whereas tophi are "rare" in primary care populations (p. 21). A similar statement is made regarding differences in comorbidity. There are no references for these observations. In general, external validity of RCTs is limited, not just in gout, so while this concern is quite valid the statement regarding tophi frequency appears to be eminence-based rather than evidence-based. Clearly, tophi are not systematically sought nor are their presence systemically documented and since most primary care based studies are based on chart abstraction or administrative data, the low prevalence of tophaceous gout in primary care may simply be a detection bias.	We agree that some of this may be detection bias, but it is certainly consistent with data from other conditions that RCTs draw a sample of patients who are more severely affected with the index condition but are otherwise healthier with respect to all other conditions when compared to patients in primary care. The proportion of patients with tophi in the major ULT RCTs are 20% (APEX), 24% (FACT), and 20% (EXCEL), and 21% (CONFIRMS). Whereas the proportion of patients with tophi in the Janssen trial, which explicitly came from primary care was 10%. Furthermore, population based estimates of the proportion of primary care patients with gout who have tophi are as low as 0.5% (246 of 52,164 patients).(PMID: 25536262) Whether this is due to detection bias is a testable question, but we can't assume it. This sentence about comorbidities was about clinical trials in general enrolling healthier patients. In the gout trials, comorbidities are not consistently reported. However as an example of this, the FACT trial of ULT reported 7% with diabetics and 10% with CVD, and patients with CKD were excluded, whereas the Janssen enrolling patients from primary care offices reported 10% with diabetes, 19% with CVD, and 23% with CKD.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Discussion/ Conclusion	3. The point is made that there is "some evidence" suggesting that ULT can be discontinued safely in some patients. The reference provided for this conclusion is the 2011 publication by Perez-Ruiz. To conclude that "ULT can be discontinued in some patients" (even when nuanced by the need for monitoring serum urate and the nuances of patient selection, which are not discussed adequately in this review) based on the available data is irresponsible and has the potential of perpetuating suboptimal gout care. In the study by Perez-Ruiz, almost 40% of gout patients experienced gout recurrence within a mean follow-up of just 2.5 years. Gout incidence is generally preceded by decades of hyperuricemia, thus recurrence in nearly half of patients in just 2-3 years does not at all support withdrawal in the average gout patient. From what we know, a patient who has tolerated years of allopurinol treatment has really negligible risk of serious AEs after having passed through the main risk window for serious cutaneous reactions. Available data suggests that rates of SUA monitoring in primary care, even after ULT initiation, are atrocious so to suggest that data exists supporting that discontinuation can be done "successfully" with appropriate serum urate monitoring is incorrect.	We have reported the evidence as it is and classified it as low strength. The need for monitoring when off ULT is stated in the text and the summary. Any clinical group developing practice guidelines from this evidence needs to keep this in mind.
TEP Reviewer #2	Discussion/ Conclusion	4. There is substantial discussion in the document around the uncertainty of risk-benefit ratios related to the long-term use of ULT. While this is true, the discussion is incomplete. This discussion, relevant to allopurinol use, should be informed by the understanding the major risk associated with this treatment (allopurinol hypersensitivity syndrome) drops precipitously with long-term use with more than 90% of these cases occurring within the first 6 months of exposure (Stamp LK et al. Arthritis Rheum 2012). Thus, if benefit was at least maintained, then one would anticipate improvements in risk-benefit with time. I believe this point should be made in the "Harms of Allopurinol" section on pg 85.	We have added evidence about the duration of use starting dose and HLA association with adverse events from allopurinol use
TEP Reviewer #2	Discussion/ Conclusion	5. On page 9 (repeated on pg 34), with mention of IL-1 targeted therapies, only anakinra is approved for the treatment of rheumatoid arthritis (the sentence suggests that both canakinumab and rilonacept are also approved RA treatments).	We have made that change to Table A and Table 1.
TEP Reviewer #2	Discussion/ Conclusion	6. On page 10, another "off label" treatment used in gout has been estrogen.	We have added estrogen as an off label agent.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Discussion/ Conclusion	7. I have concerns about the statement on page 17 (covered again on pg 53-54) regarding adverse effects of steroids primarily relating to "long-term use" with the suggestion these aren't an issue in gout. The statement is made that AEs are both dose and duration dependent, but this really ignores cumulative dose. This is mentioned for the first time on pg 54, but this point should be made more boldly. Cumulative steroid exposure is quite relevant for gout patients being treated repeatedly in this fashion. Gout is frequently accompanied by metabolic syndrome and in addition to adverse effects noted, there are significant risks in terms of cardiovascular risk, hypertension and dyslipidemia. With frequent use and high cumulative exposure risks often associated with chronic use (bone loss, cataracts, etc) likely become relevant as well.	We have added this information to that section
TEP Reviewer #2	Discussion/ Conclusion	8. Table 1, pg 34, Colcrys is now owned by Takeda and not URL.	Thank you. We have made this change in Table A and Table 1
TEP Reviewer #2	Discussion/ Conclusion	9. Point of clarification - Discussed on page 35, recent ACR guidelines included task force members that were from primary care and the intended audience for those guidelines included primary care providers.	We have added that the ACP committee (which also include a Rheumatologist) is "mainly" PCPs.
TEP Reviewer #2	Discussion/ Conclusion	10. On page 78 of report, in discussing Zhang 2010 et al (ref 90) would put quotations around "cure rate" to show this was a term used by authors.	We have made this change
TEP Reviewer #2	Discussion/ Conclusion	11. In the summary of studies examining dietary and weight loss interventions (p. 45), the working group may want to review Dalbeth N et al. Annals Rheum Dis 2014; 73: 797-802. This study showed urate-lowering effects of weight loss following bariatric surgery (included a small sample with known gout).	Yes, thank you. We have added the findings of this study to our response to KQ2.
TEP Reviewer #2	Discussion/ Conclusion	12. Should the title of Table 8 (pg 78) be "dietary interventions" rather than pharmacologic therapies?	We have made that change
TEP Reviewer #2	Discussion/ Conclusion	13. In regards to ULT "key points" (p. 86) rather than saying "ULT does not reduce the risk of acute gout attacks in the first six months" it seems to me that it would be helpful to phrase this in a slightly more optimistic way, something like "The strength of evidence is high that ULT must be given for at least 6 months or longer in order to yield clinical improvements such as a reduction in acute gout flares."	The statement in the report reflects the evidence in the RCTs. In fact, no RCT has yet shown a reduction in acute gout attacks, so we can't revise this statement as suggested by the reviewer.
TEP Reviewer #2	Discussion/ Conclusion	14. In discussing the effectiveness and comparative effectiveness of allopurinol vs. febuxostat (beginning on pg 98), existing uncertainly relates at least in part to study designs that failed to incorporate allopurinol doses above 300 mg daily even though the drug is approved at daily doses up to 800 mg. These same studies also studied only fixed dose ULT, in contrast to guideline recommendations for low dose initiation followed by; titration. This represents a major flaw of those studies and needs to be mentioned.	We agree that this is a limitation, which is why we did not emphasize the differences in outcomes between 80mg of febuxostat and 300mg of allopurinol because that was felt to be a non-equipotent comparison.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Discussion/ Conclusion	15. Page 98 – I would not refer to serum urate as a "non-clinical biomarker". This is confusing as serum urate level is routinely used in clinic; it is a clinical measure, not just a research biomarker.	We have changed this to research biomarker.
TEP Reviewer #2	Discussion/ Conclusion	16. Since this report helps to identify the research agenda, I think it would be helpful in the discussion of prophylaxis to specifically say that there have been no controlled studies to date examining the use of steroids in this arena (this question will naturally come up since this drug is widely used for acute attacks and is indeed used for prophyalxis in patients with contraindications to the other 2 agents).	This was added to the research agenda
TEP Reviewer #2	Discussion/ Conclusion	17. On page 114, typo in first paragraph under "Detailed synthesis" – should say "did assess serum uric acid".	This typo was corrected.
Peer Reviewer #3	Discussion/ Conclusion	yes	Thank you
TEP Reviewer #3	Discussion/ Conclusion	The future research section is labeled as 'research gaps'; most of these are clear and easily translated, though some of them appear to not be practical because of overwhelming empiric scientific/biologic evidence and attractive benefit:risk ratio.	No response necessary. The reviewer is expressing her opinion.
TEP Reviewer #4	Discussion/ Conclusion	8. Research Gaps The corresponding section of research gaps could be strengthened regarding the absence of credible nutrition therapy trials that actually implement and measure fidelity of common nutrition interventions for treatment of gout and reduction in acute gout attack. It may be helpful to clearly articulate the dietary components that need testing:. E.g. impact of low purine diet (low fat, reduction in protein and purine containing foods), energy restriction/weight reduction, adequate hydration, restriction of alcohol, restriction of high fructose corn syrup and increase in lowfat dairy.	In the section entitled, Research Gaps, we provided recommendations regarding several of the dietary components. We have added the rest and strengthened the wording.
TEP Reviewer #5	Discussion/ Conclusion	Please see general comments, particularly with regard to inclusion of comparative efficacy and comparative safety as a research gap.	No response necessary

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #6	Discussion/ Conclusion	1. ES-14: Key findings and SoE: I can appreciate that you are making a logical deduction in making your conclusion that SoE for steroids is high. Can we use a similar logical deduction without strong evidence about the utility of lowering SUA below a particular threshold (i.e., target)? I believe that this is what rheumatologists and the FDA have been doing as discussed above.	We think these two situations are different. We do judge -using a logical argument, and in the absence of direct evidence - that lowering SUA with ULT will reduce acute gout flares has a "moderate" SoE. However, we cannot judge that the evidence is at least moderate that a "one-size-fits-all" threshold for SUA for all patients, because such strategies have failed, despite randomized controlled trials in other conditions, such as diabetes and hypertension, despite those conditions having a similar logical argument.
TEP Reviewer #6	Discussion/ Conclusion	2. ES-14, line 53: Is the statement "Tophi are rarely seen in primary care settings" based on some evidence or is it anecdotal? I would think PCPs and ED physicians are not carefully looking for subtle tophi or signs for intra-articular tophi (manifested by joint ROM limitations), which would require an MSK exam of at least frequently involved joints and areas. I would say that this statement is probably at the level of insufficient SoE.	The proportion of patients with tophi in the major ULT RCTs are 20% (APEX), 24% (FACT), and 20% (EXCEL), and 21% (CONFIRMS). Whereas the proportion of patients with tophi in the Janssen trial, which explicitly came from primary care was 10%. Furthermore, population based estimates of the proportion of primary care patients with gout who have tophi are as low as 0.5% (246 of 52,164 patients).(PMID: 25536262) Whether this is due to detection bias is a testable question, but we can't assume it.
TEP Reviewer #6	Discussion/ Conclusion	3. ES-16, line 9-10: I recommend modifying the statement about the increased risk of flares associated with ULT initiation. It is important to note that this happens when your initial dose is high (e.g., allopurinol 300 mg or febuxostat 80mg daily). As demonstrated in the aforementioned paper by Rees et al., a low-dose initiation incremental escalation approach would not necessarily trigger an increased risk of gout flares. It is also important to remind the PCPs that this increased risk is transient, happening only within the initial few months due to well-established pathophysiology (i.e., mobilization of urate crystals), and thus, prophylaxis during this initial period is recommended unless you were to adopt a low-dose approach as above. As written, the line seems to send a somewhat misleading message to PCPs.	We have revised this sentence to be similar to the revised sentence in the abstract.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Clarity and Usability	Overall well written and usable. Thank you.	Thank you
Peer Reviewer #1	Clarity and Usability	Some discussion of the extent to which the findings are, or are not, congruent with current guidelines would be helpful. I know the EPC reports are not guidelines, but the context would be helpful.	Guidelines are explicitly a combination of evidence and judgment. Our evidence report is explicitly only the evidence. We are prohibited from adding the judgment that is necessary to state whether our findings are or are not congruent with current guidelines.
TEP Reviewer #1	Clarity and Usability	I must have missed something but why are there essentially TWO papers that are not quite the same but cover nearly identical material?	One of these is the Executive Summary and one is the main report. When the report is finally published they will be separated and the ES will be a standalone document.
TEP Reviewer #1	Clarity and Usability	here are a few random comments: I found a couple of places where the recommendations are different than the relatively recent ACR GL. Perhaps these should be highlighted (diet doesnt seem to do much (this is different than common wisdom, perhaps some explaination is in order?), Role of stopping therapy)	This evidence report does not make recommendations, therefore we can't compare to the ACR recommendations.
TEP Reviewer #1	Clarity and Usability	Page 9 line 47: URL phrma is no longer the only supplier of colchcine.	Thank you. We have revised the name to Takeda.
TEP Reviewer #1	Clarity and Usability	Page 9 line 57, Savient is no longer in business, filed chapter 11 in Oct 2013. Krystexxa is not marked by a new firm Crealta.	Thank you. We have revised the name of the manufacturer to Crealta.
TEP Reviewer #1	Clarity and Usability	in the first run thru PIOCOT and GRADE are not defined, they are in the second paper.	The PICOTs and GRADE definitions are not in the ES. They are defined in the main report due to space limitations of the ES.
TEP Reviewer #1	Clarity and Usability	KQ3b (p.52) [High strength of evidence supports animal-derived ACTH formulation to reduce pain in acute gout] is a great question but it is not answered in the text!!	Key Question 3b is about treatment of chronic gout but the ACTH studies are about the treatment of acute gout, so we do not understand the question and cannot respond to it.
TEP Reviewer #1	Clarity and Usability	KQ for next time: WHEN do allopurinol rxns occur? early late or at changes of dose or anytime? My reading of the scant literature, especially on Allopurinol Hypersensitivity Syndrome suggests that it is early.	We have added this to the Research Gaps

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	Clarity and Usability	I was surprised to read that monitoring doesnt improve outcomes. This goes against a great deal of data (especially when one considers that COMPLIANCE is much better with interactions with medical staff which in turn helps patients acheive TTT goal of <6mg/dl which is known to improve outcomes)	Our evidence report does not conclude that monitoring does not improve outcomes. Rather we found no evidence that monitoring improves outcomes and the only evidence about adherence did not support a positive association. However, we have acknowledged that monitoring is the only way to determine if ULT is having an effect on SUA and have added this to the summary.
Peer Reviewer #2	Clarity and Usability	The report is well structured and clear in its presentation.	Thank you
TEP Reviewer #2	Clarity and Usability	Overall, I found the report to be well structured and organized. The main points / key findings are clearly outlined and quite easy to find. As outlined above, I believe this document has the potential to be a very valuable resource in gout.	Thank you
Peer Reviewer #3	Clarity and Usability	yes	Thank you
TEP Reviewer #3	Clarity and Usability	The structure and organization is fine. There were some minor comments that I provided in relevant areas.	Thank you
TEP Reviewer #4	Clarity and Usability	7. Characterization of answers to questions – Key points Rather than citing "strength of evidence" from RCTs when it doesn't appear to be any research to address the topic, it may be more appropriate to state that there do not appear to be ANY RCTs that actually tested common nutrition therapy in its entirety.	We have changed the strength of evidence to insufficient.
TEP Reviewer #4	Clarity and Usability	The only RCT involved dietary advice, and in that study the patients 1 of 15 in control group self reported making any modifications in their diet and 7 in intervention group reported making any changes, however there doesn't appear to be any quantification of what if any actual changes in dietary intake occurred….and the second intervention was weight reduction which is actually one component of nutrition therapy for Gout… From all of this it might even appear that the most appropriate statement is that there is REALLY no research and certainly no RCTs that actually test the common NUTRITION THERAPY COMPONENTS, only one that tests the provision of dietary advice….thus there appears to be NO evidence by which to judge effectiveness of the dietary components…..This doesn't mean that it isn't effective, it means we DON"T KNOW. Lack of evidence is not the same as lack of effectiveness or low strength of evidence…it is LACK of any research. Isn't it impossible to judge strength of evidence when there IS no evidence?	Yes, the reviewer is correct that lack of evidence is not the same as lack of effectiveness. We have changed the strength of evidence to insufficient.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Clarity and Usability	The report is very well-written and organized, and I think it is useful. Hopefully this is the last SR the world will ever need covering the topic of placebo-controlled trials for acute gout, since (as the authors point out) it hasn't really been ethical to do a new one for the past 40 years or more.	Thank you
Carol Alter, AstraZeneca	General	Multiple societies and groups such as ACR, EULAR, 3e, and the British SGAWG support the concept of treat to target (see references 1-4 listed below). 1 Zhang W, Doherty M, Bardin T, et al; EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2006;65):1312-1324. [EULAR 2006] 2 Khanna D, Fitzgerald JD, Khanna PP, et al; American College of Rheumatology. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken). 2012;64:1431-1446. [ACR 2012] 3 Sivera F, Andrés M, Carmona L, et al. Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative. Ann Rheum Dis. 2014;73(2):328-335. [3e Initiative 2014] 4 Jordan KM, Cameron JS, Snaith M, et al; British Society for Rheumatology and British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group (SGAWG). British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. Rheumatology (Oxford). 2007;46:1372-1374. [BSR 2007] Specifically, the American College of Rheumatology recommends: > sUA levels <6 mg/dL are recommended for all patients with gout1-3, and even <5 mg/dL to improve signs and symptoms of gout2 > Consistently maintaining sUA levels <6 mg/dL can keep patients below the saturation point of uric acid, preventing further crystal formation and > Deposition1, and targets <5 mg/dL can accelerate dissolution of crystals in patients with more advanced disease3,4	We understand these societies support this concept. As we note, though, this concept has not been formally tested as treat to target strategies have been tested for diabetes and for blood pressure and for lipids.

Commentator & Affiliation	Section	Comment	Response
Carol Alter, AstraZeneca	General	The AHRQ review does not take into account that gout is a chronic inflammatory disorder resulting from crystal deposition. Conclusions focus on data that assess the effect of urate lowering therapy over a short time frame; e.g. ≤12 months. Assumptions are made that there is subsequently minimal effect on resolution of flares or tophi. The report does not assess the long term impact of maintaining sUA below 6 mg/dl on the resolution of tophi and symptomatic flares. We would like to present data from RCTs, smaller interventional trials and observational research dating before 2010 as well as after 2010 that include a large body of evidence to strongly suggest that reducing sUA to a target level over several years reduces gout flares and results in tophi resolution.	As noted in our report, we found no randomized clinical trial data reporting long term results.
Carol Alter, AstraZeneca	General	The AHRQ review classifies gout patients who have not had a recent gout flare as “asymptomatic”. This classification is strictly clinical. During periods between flares, recent data utilizing enhanced imaging with DECT (dual-energy CT) scans, show continued uric acid crystal deposition in symptomatic and asymptomatic joints that strongly correlates with bony erosions seen on X-ray. This has been labeled by some as “subclinical” gout. This evidence supports the ongoing damage of uric acid crystal deposition on joints over time.	"Asymptomatic" is by definition a term used if a patient is not having symptoms. Lab and x-ray changes in the absence of symptoms are still "asymptomatic" and are of questionable clinical significance unless they can be proven to be associated with subsequent symptoms for which the evidence outside of recurrent gout flare is as yet unproven for serum urate.
Carol Alter, AstraZeneca	General	Reference 1: McCarthy GM, et al. Influence of antihyperuricemic therapy on the clinical and radiographic progression of gout. Arthritis Rheum. 1991; 34:1489-1494. • Study of 3 cohorts of patients grouped based on pattern of gout disease on ULT (allopurinol, probenecid, or both) - Group A: 14 patients with no tophi on physical examination or radiographic evidence of gouty - Group B: 11 patients with no tophi on physical examination, but with radiographic evidence of gout - Group C: 14 patients with classic tophaceous gout (tophi on physical examination and radiographic evidence of gout). • Of the 14 patients in group C, 7 patients with reduced tophi on physical examination had mean sUA levels of 6.2 mg/dL, compared with 7 patients with increased or unchanged tophi who had mean sUA levels of 8.2 mg/dL (P<0.02) • sUA levels correlated with clinical tophaceous deposit; therefore, patients with lower mean sUA levels were more likely to experience tophi reduction • Physicians treating gout advised to reduce patients’ sUA to ≤6 mg/dL and to monitor efficacy by observing the frequency of acute flares, as well as the reduction in tophi and prevention of joint deformity	We excluded this study as a non-systematic review.

Commentator & Affiliation	Section	Comment	Response
Carol Alter, AstraZeneca	General	Reference 2: Perez-Ruiz F, et al. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. Arthritis Rheum. 2002;47:355-360. • Prospective, observational study of 63 patients with tophaceous gout started on ULT (allopurinol, benzbromarone, or both) - Mean baseline sUA level 8.98 ± 1.43 mg/dL before ULT • Mean time from onset of ULT to disappearance of the target tophus for the entire series was 20.8 ± 10.2 (range 6-64) months • Mean sUA levels during followup on ULT - 5 patients with sUA levels 6.1-7.0 mg/dL showed a reduction of 0.53 ± 0.59 mm/month - 19 patients with sUA levels 5.1-6.0 mg/dL achieved a reduction of 0.77 ± 0.41 mm/month - 19 patients with sUA levels of 4.1-5.0 mg/dL had their tophi reduced by 0.99 ± 0.50 mm/month - 20 patients with sUA levels ≤4.0 mg/dl showed a velocity of reduction of tophi of 1.52 ± 0.67 mm/month • There was a linear relation between sUA level and reduction in tophi • During follow-up, when sUA levels were maintained below the threshold for UA saturation (7.0 mg/dL), all patients were cleared from tophi	We excluded this study as it is not a randomized controlled trial.
Carol Alter, AstraZeneca	General	Reference 3: Li-Yu J, et al. Treatment of chronic gout. can we determine when urate stores are depleted enough to prevent attacks of gout? J Rheumatol. 2001;28:577-580. • Prospective study of 57 male patients with gout (confirmed by identification of MSU crystals on knee synovial fluid analysis at baseline) treated with ULT (allopurinol) to target sUA of ≤6.0 mg/dL, and maintained for at least 12 months, at which time knee synovial fluid analysis was repeated • After 12 months of ULT, 67% of inadequately treated patients (with sUA levels maintained >6.0 mg/dL) had a mean of 6 gout flares, compared with 33% of adequately-treated patients (with sUA levels ≤6.0 mg/dL) who had a mean of 1 gout flare • Depletion of urate crystals from knee synovial fluids could be achieved if the sUA was maintained <6.0 mg/dL for at least 12 months	We excluded this study for not addressing the Key Question.

Commentator & Affiliation	Section	Comment	Response
Carol Alter, AstraZeneca	General	Reference 4: Yamanaka H, et al. Optimal range of serum urate concentrations to minimize risk of gouty attacks during anti-hyperuricemic treatment. Adv Exp Med Biol. 1998;431:3-8. • Retrospective analysis of 350 patients with gout on ULT • With sUA levels maintained between 4.6-6.6 mg/dL, the risk ratio of a gout flare was 0.705, compared with sUA levels maintained outside of this range • Proposed that sUA levels should be maintained within this range during the initial 6 months of ULT	We excluded this study for not addressing the Key Question.
Carol Alter, AstraZeneca	General	Reference 5: Shoji A, et al. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. Arthritis Rheum. 2004;51:321-325. • Prospective study of 267 patients with gout who have experienced at least 1 gout flare and not taking ULT (allopurinol, benzbromarone, or both) at first clinic visit, observed for up to 3 years • Adjusted for baseline sUA levels and number of gout flares prior to the observation period - Recurrence of flares was associated with average sUA levels during the observation period with an odds ratio (OR) of 0.42 (P<0.001) - ULT decreased the risk of recurrent flares by reducing average sUA levels with an OR of 0.22 (P<0.001) • Mean average sUA levels in the patients in the medication group who experienced recurrent flares was only 7.01 mg/dL, whereas those in the no-attack subgroup averaged 6.36 mg/dL, suggesting that 7 mg/dL is not a suitable sUA target • Among 81 treated patients with average sUA levels <6.0 mg/dL, 71 patients (86%) had no recurrent flares during the 3 year observation period	We excluded this study for not addressing the Key Question.

Commentator & Affiliation	Section	Comment	Response
Carol Alter, AstraZeneca	General	Reference 6: Perez-Ruiz F, et al. Using serum urate levels to determine the period free of gouty symptoms after withdrawal of long-term urate-lowering therapy: a prospective study. Arthritis Rheum. 2006;55:786-790. • Prospective, long-term, follow-up study of 104 patients with gout treated with ULT (allopurinol, benzbromarone, or both) during a 5-year period • Mean baseline sUA levels 8.76 ± 1.19 mg/dL (median 8.49 mg/dL) • Kaplan-Meier analysis for survival demonstrated that patients in the highest ranges of sUA levels had the poorest outcome (just over 2 years without symptomatic gout), compared with patients in the lowest sUA range who had symptom-free durations averaging >4 years • Implications for clinical practice: - sUA levels should be reduced enough for a prolonged period of time to deplete urate burden (goal of ULT should be reduction of average sUA to subsaturation levels) - Patients with average sUA levels of <7.0 mg/dL for at least a 5-year period are likely to achieve prolonged asymptomatic disease after ULT withdrawal	We have now included this study in our review
Carol Alter, AstraZeneca	General	Reference 7: Sarawate CA, et al. Serum urate levels and gout flares: analysis from managed care data. J Clin Rheumatol. 2006;12:61-65. • Retrospective, observational study of a managed care database of 5942 patients with gout • Of the patients on ULT (allopurinol, probenecid, or sulfinpyrazone), patients with nontarget sUA levels were 59% more likely to flare than those at target (≤6.0 mg/dL) • Allopurinol users who were not at target were 75% more likely to flare	We excluded this study as it is not a randomized controlled trial.
Carol Alter, AstraZeneca	General	Reference 8: Halpern R, et al. The effect of serum urate on gout flares and their associated costs: an administrative claims analysis. J Clin Rheumatol. 2009;15:3-7. • Retrospective administrative claims analysis of 18,243 patients with gout (4277 patients with available sUA data) • Logistics regression results demonstrated that patients with baseline sUA ≥6.0 mg/dL relative to sUA <6.0 had 1.3 times the odds of gout flare (P<0.05)	This study was included under KQ4b.
Carol Alter, AstraZeneca	General	Reference 9: Wu EQ, et al. Frequency, risk, and cost of gout-related episodes among the elderly: does serum uric acid level matter? J Rheumatol. 2009; 36:1032-1040. • Data from the Integrated Healthcare Information Services claims database of 2237 patients with gout • Compared with patients with normal sUA levels (<6 mg/dL), patients with high (6-8.99 mg/dL) and very high (>9 mg/dL) sUA levels were more likely to develop a flare within 12 months (OR 2.1 and 3.4, respectively) • In multivariate regressions, the average annual number of flares increased by 11.9% with each unit- increase in sUA level above 6 mg/dL (P<0.0001)	This study was included under KQ4b.

Commentator & Affiliation	Section	Comment	Response
Carol Alter, AstraZeneca	General	Reference 10: Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med. 2005;353:2450-2461. The figure below illustrates the reduction seen regarding flare rates in the last 4 weeks (wks 48-52) of FACT after 1 year of ULT. (See Figure 2 in Carol Alter's comments doc.)	This study was included in KQ3.
Carol Alter, AstraZeneca	General	Reference 11: Becker MA, Schumacher HR Jr, MacDonald, PA, et al. Clinical efficacy and safety of successful longterm urate lowering with febuxostat of Allopurinol in subject with gout. J Rheumatol 2009;36;1273-1282. Figure 3 demonstrates following 18 months of ULT therapy gout flares dramatically decrease and at 3 years follow up proportion of subjects with a gout flare approached zero (0). Figure 4: At 3 years follow up, maintenance of sUA <6.0 mg/dl resulted in significant reduction in both size and number of tophi. (See Figure 3 and 4 in Carol Alter's comments doc.)	This study was included in KQ3.
Carol Alter, AstraZeneca	General	Reference 12: Dalbeth N, Opetaia A, Kalluru R, et al. Relationship between structural joint damage and urate deposition in gout: a plain radiography and dual-energy CT study. Ann Rheum Dis 2015;74:1030–1036. "MSU crystal deposition was more frequently observed in joints with erosion, JSN, spur, osteophyte, periosteal new bone and sclerosis. A strong linear relationship was observed in the frequency of joints affected by MSU crystals with radiographic erosion score. The number of joints at each site with MSU crystal deposition correlated with all features of radiographic joint damage. In linear regression models, the relationship between MSU crystal deposition and all radiographic changes except JSN and osteophytes persisted after adjusting for subcutaneous tophus count, serum urate concentration and disease duration. MSU crystals are frequently present in joints affected by radiographic damage in gout. These findings support the concept that MSU crystals interact with articular tissues to influence the development of structural joint damage in this disease."	We excluded this study for not addressing the Key Question.

Commentator & Affiliation	Section	Comment	Response
Carol Alter, AstraZeneca	General	Reference 13: Dalbeth N, Stamp L. Hyperuricaemia and gout: time for a newstaging system? Ann Rheum Dis 2014;73:1598-1600. "Revision of the hyperuricaemia and gout clinical staging system would have a number of advantages. First, the revised system would provide a rational basis for testing the potential role for screening of symptomatic disease, both serum urate concentrations in those at high risk of hyperuricaemia (eg, those with metabolic syndrome, chronic kidney disease and/or heart failure, those on diuretics, solid organ transplant recipients, and those with a family history of gout); and in those with severe hyperuricaemia, imaging methods to detect features of asymptomatic MSU crystal deposition. At present, the benefits of such screening are not certain, and research to examine the role of screening in asymptomatic disease is required. Furthermore, this proposed revision provides a clear focus on gout as a chronic disease of MSU crystal deposition, and emphasizes the importance of targeting the underlying basis of disease in order to achieve dissolution of MSU crystals and 'cure' of gout. Finally, this staging system would allow assessment of the potential role of early intervention for presymptomatic disease, particularly those with Stage B disease (MSU crystal deposition but without signs or symptoms of gout)."	We excluded this study for not addressing the Key Question.
Carol Alter, AstraZeneca	General	Summary: The totality of the evidence to date supports the notion that urate lowering therapy provides clinically meaningful benefits to patients beyond sUA lowering. As gout is a chronic crystal deposition disease, benefits are not typically seen in gout flare reduction before 18 months, while tophi reduction may take up to 5 years. We appreciate the opportunity to provide these comments. Again, please feel free to contact me if additional information is needed.	Thank you
Eisenberg Center	Background	This systematic review aimed to assess the evidence related to the treatment of acute and chronic gout. Given the large number of pharmacological and non-pharmacological treatment strategies used in clinical practice, the authors of the review have done an excellent job of summarizing the available evidence and presenting the findings in summary tables. We would like to highlight a few items that we felt were not immediately clear and might present challenges for audiences for whom we plan to translate this review (clinicians and consumers): • The types of interventions used in the treatment of acute and chronic gout are described in the background section. However, additional detail regarding how current practice is directed by guidelines would be very helpful. Clinicians and guideline developers might seek information on what new insights come from this systematic review and how the findings align or do not align with current recommendations.	We don't understand the meaning of this phrase "additional detail regarding how current practice is directed by guidelines". Does this mean "what are the recommendations of guidelines?" or does it mean "How does current practice comport with the recommendations from guidelines?" If the former, we could briefly summarize the recommendations from ACR/EULAR and no others. The latter is outside the scope of this review.

Commentator & Affiliation	Section	Comment	Response
Eisenberg Center	General	• The question of when to use particular medications may likely arise from our audiences. Specifically, they might be interested in knowing if any studies assessed the efficacy of pharmacological interventions at differing time points after initiation of the flare as such information may assist in decision making (for e.g., some authors in the gray literature have pointed to the need for initiation of colchicine in the first 12-24 hours).	This was assessed, as it is in Key Question 1c, and reported in subgroups, but we revised the text to make it more clear.
Eisenberg Center	General	• Among users of the translation products there is likely great interest in non-pharmacologic interventions. Despite the limited evidence for the efficacy of non-pharmacological interventions that the systematic review provides, one might expect that dietary and lifestyle changes might be commonly recommended for many reasons. Could the authors provide additional details regarding the concomitant use of dietary and lifestyle recommendations (e.g. weight loss, reduction of fructose containing beverages, limiting alcohol intake, etc.) and whether there are any harms to such recommendations?	We can only report any harms that were reported in the original studies. To our knowledge no harms were reported for any of the dietary interventions.
Eisenberg Center	General	• It is unclear what types of co-interventions gout patients were receiving concomitantly in the various studies and the likely impact of such co-interventions on the effectiveness and/or harms of the interventions assessed. For example, in patients receiving pharmacological therapies, was advice on dietary or lifestyle changes (reduced alcohol consumption, smoking cessation, etc.) commonly provided even if the efficacy of such interventions are unsubstantiated?	This issue of co-interventions such as dietary advice is not relevant for acute gout treatment. No RCT of chronic gout management made any mention of any dietary or lifestyle advice.
Eisenberg Center	General	• The authors have provided a useful and helpful summary of the adverse effects associated with the various pharmacological therapies. Would it be possible to expand the descriptions to include additional details regarding the important contraindications of the various therapies? Such descriptions will address questions that commonly arise in testing of translation products, particularly with clinicians, and will increase the credibility and usefulness in their view.	We have added additional text
Melissa Starkey, American College of Physicians	General	13. There was not much about allopurinol hypersensitivity syndrome/DRESS. It is an uncommon enough occurrence that the lack of finding of increased risk in trials is not surprising. But, when it occurs, it can be severe and even fatal. It would be great to know if there were observational study data on the frequency of this type of severe AE, and whether it is dose dependent.	We have added additional detail on DRESS

Commentator & Affiliation	Section	Comment	Response
Melissa Starkey, American College of Physicians	Executive Summary	1. ES-2-In the review of chronic gout, is there any information about natural history; for example, the probability of developing tophi over time, and more importantly, the probability of developing kidney disease including symptomatic kidney stones? These data might support or refute a "preventive" argument for treating hyperuricemia, as opposed to simply controlling gout symptoms.	Natural history was not one of the Key Questions and was not part of the systematic review, but we have added some text from secondary resources on this.
Melissa Starkey, American College of Physicians	Executive Summary	3. ES-5-Similarly, should the final health outcomes include chronic kidney disease and kidney stones?	The analytic framework was developed, peer-reviewed and accepted at the Topic Refinement stage and cannot be changed now. However, we did examine our included studies for renal outcomes and added these to the text.
Melissa Starkey, American College of Physicians	Executive Summary	4. ES-12- Any evidence related to the change of natural history of gout from urate-lowering therapy. Any effect on the development of chronic arthritis, nephrolithiasis, chronic kidney disease. If not, the "preventive" argument for treatment is weak.	No controlled trials evidence was found assessing these outcomes
Melissa Starkey, American College of Physicians	Background	5. Page 2- Again, any estimates of the quantitative risks over time of nephrolithiasis and chronic interstitial nephropathy? What is the correlation between tophi and symptoms?	This was not in the Key Questions, so we looked outside of our review process for these data but could not find risk-over-time estimates. We ask, however, that the clinicians we talked to state that patients consider the cosmetic appearances of tophi to be sufficient reason to want them removed/dissolved.
Melissa Starkey, American College of Physicians	Discussion	12. (pg. 89) In the applicability paragraph, they note that people with comorbidities are more often excluded, but I can't find where they report on what they found in their SR regarding this point for the included gout studies. This is information that is ascertainable and able to be reported.	This sentence was about clinical trials in general enrolling healthier patients. In the gout trials, comorbidities are not consistently reported. However as an example of this, the FACT trial of ULT reported 7% with diabetics and 10% with CVD, and patients with CKD were excluded, whereas the Janssen enrolling patients from Dutch primary care offices reported 10% with diabetes, 19% with CVD, and 23% with CKD.

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Melissa Starkey, American College of Physicians	Results Key Question 1a	14. (pg 19) One way of diagnosing gout was to give an empiric trial of colchicine. This was based on the concept that colchicine helps little else but gout and pseudogout. It is possible that clinicians perceive this to be a benefit of colchicine over other modalities. If there is no evidence in the literature search to support that notion, perhaps they could mention that specific finding in their response to Key Question 1a.	We didn't find any evidence that examined the preferences for colchicine based on its possible utility as a diagnostic agent although we did not search for such evidence systematically since it was not in the PICOT was such evidence systematically
Melissa Starkey, American College of Physicians	Results Key Question 3	7. Page 52- In the reviewer's mind, a key question for clinicians to be addressed in a guideline is whether therapy can be symptom driven, or whether there are preventive concerns. If occasional or even frequent acute flares are treated episodically, is there any price to be paid in terms of the development of chronic arthritis (not just tophi), nephrolithiasis or CKD. Any evidence on the magnitude of these risks and whether urate lowering changes them? Even confirmation of the absence of evidence would be very helpful.	There is no controlled trial evidence of treatment improving these outcomes other than flare. However, there is a large body of observational evidence relating elevated serum urate to many health outcomes.
Melissa Starkey, American College of Physicians	Results Key Question 3	8. Page 67- Any evidence linking tophi to symptoms? Faster or more complete resolution of tophi does not necessarily sound like a patient-centered outcome without concomitant improvements in symptoms.	Tophi are usually reported as their own outcome. Clinicians' experience with patients with visible tophi are that they value the cosmetic benefit.
Melissa Starkey, American College of Physicians	Results Key Question 3	9. Are any comparative cost effectiveness data for gout treatments available?	Cost effectiveness is excluded from this evidence report
Melissa Starkey, American College of Physicians	Results Key Question 3	10. (pg. 77) There is little mention of probenecid, can you address this?	We have added text explaining why probenecid use has fallen from favor
Melissa Starkey, American College of Physicians	Results Key Question 3	11. (pg 52) In the key findings for KQ 3, there is no discussion of the evidence for subgroups or the adverse event rates of the drugs (they do note there is no difference between the two drugs in terms of ADE). This is reported for KQ1, and I think parallel information would be helpful in KQ3.	We have added bulleted pointes for our findings on adverse events for KQ3.

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Confidential Public Reviewer	General	1. This draft work is not sophisticated enough re gout disease pathophysiology and true treatment to effective target for disease modification, as opposed to gout symptom management, and therefore falls short of the quality of care of specialty society derived guidelines (such as ACR guidelines that included significant participation by primary care, nephrology and patient advocate repesentatives in the task force panel, and EULAR specialty society guidelines) such as for rheumatoid arthritis treat to target, let alone gout treat to target, which target true disease modification. In the case of gout, the only true disease modification is promotion of dissolution of the offending inflammatory stimulus, ie, tissue deposits of urate crystals, and the only proven way of doing that effectively is urate lowering therapy (ULT) prolonged enough and to a serum urate level low enough (ie, well enough below the saturability threshold for monosodium urate of 6.8-7.0 mg/dL) to steadily diminish urate crystal deposits.	This evidence report was primarily focused on patient clinical outcomes. Serum urate was included as an outcome, but it is not the primary outcome. These decisions were made at the Topic Refinement stage.

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Confidential Public Reviewer	General	2. The majority of clinical trials with oral ULT, indeed as cited by the AHRQ draft review, are not long enough in the non-extension phase before open label extensions, to achieve measurable decrease in palpable tophi, and associated articular urate crystal deposits and flares of acute arthritis typically take longer than a year to significantly improve in such clinical trials. Moreover, remodeling of tissue urate crystal deposits, particularly in the early phase of ULT, is clearly pro-inflammatory, with linkage to marked early increase in acute gout flares (eg, in the FACT trial with both allopurinol and febuxostat, and also in the pegloticase program trials early phase). However, this does not mean that the scope of practice of primary care providers for FDA-approved agents should not include an effort to achieve and maintain, and monitor a serum urate level (surrogate marker for body urate burden) low enough for disease modification. Ample clinical research in the last decade, largely separate from large pharma-sponsored clinical trials, has indicated that a serum urate level of <6 mg/dL at a minimum, and not adequately cited by the AHRQ review, achieves both imaging (ultrasound, dual energy CT) and synovial fluid crystal analysis detectable decreases in articular urate crystal deposits. The particularly robust urate-lowering effect of pegloticase, when maintained over time, also is a striking and clear example that with dissolution of tissue urate crystal deposits, acute gout flare rates go significantly down with time and health related quality of life goes significantly up. Hence, the statement in the AHRQ report that "strength of evidence is low that treating to a specific target serum urate level reduces the risk of gout attacks" is far off the mark, and does not support adequate gout quality of care, even at the scope of the primary care level. Essentially, the current report risks boxing in primary care providers to inferior quality of care for gout by advocating for acute symptom control rather than long term disease modification. This is an obsolete and backward looking nihilistic strategy, that neglects major advances in gout clinical research in the last decade. It also overlooks a mountain of evidence that patients with gout have higher disease-associated systemic morbidities (including CAD, hypertension, and CKD progression), and mortality rates, particularly with tophaceous and polyarticular disease, and also contributed to by undertreatment of uric acid compared to xanthine oxidase inhibitor treatment, and likely impacted by toxicities of NSAIDs most popularly employed to repeatedly treat acute gout flares.	As explained in the draft report, a treat-to-target approach would require RCT level evidence of that strategy in order to be considered high strength evidence. Diabetes, hypertension, and hyperlipidemia all also had strong observational evidence supporting associations with various adverse outcomes, had RCT evidence showing that lowering A1C, blood pressure, and LDL resulted in improved outcomes, all had one-size-fits-all treat-to-target management strategies advocated by respected professional societies, and all three treat-to-target strategies, when actually tested in RCTs, were found to produce less benefit and more harm than predicted. Therefore, we judge that, in gout, a treat-to-target strategy will require RCT level of evidence for support before this EPC can rate it as strong evidence. The concern about lowering SUA to less than 6 is not the physiologic effects on the body but rather the increased risk of side effects, monitoring, and time associated with intensified treatment.
Confidential Public Reviewer	General	3. There is ample evidence in the literature, not adequately assessed by AHRQ, of gout patient nonadherence to ULT, and a core method of assessing adherence is regularly looking at the serum urate level (eg once to twice per year). This is a core recommendation of the 2012 ACR gout management guidelines.	We need the reviewer to identify this evidence in order to respond to this critique.

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Confidential Public Reviewer	Executive Summary	4. The definition of “chronic gout” on page 9 (ES-2) is inadequate in the AHRQ document, especially since articular and tendinous tophi can be demonstrated by advanced imaging (dual energy CT and ultrasound) well before palpable and visible subcutaneous tophi appear. In this sense, nearly all symptomatic gout can be identified to already be tophaceous.	The term "chronic gout" was set originally at the time of Topic Nomination, was vetted by Key Informants during the Topic Refinement process, was vetted again during the public posting of the protocol, and cannot be changed now. Furthermore the term "chronic gout" is used in the literature (for example, in the 2014 Cochrane review co-authored by Rachelle Buchbinder, Claire Bombardier, and other noted rheumatologists).
Confidential Public Reviewer	General	5. The statements of AHRQ on the literature for low dose colchicine not being convincingly superior to high dose colchicine for acute gout re the risk:benefit ratio (taking into consideration efficacy and adverse events) are harmful to quality of care. Such evidence is clear from the highest level of evidence, ie, large randomized clinical trial evaluation. Moreover, the low dose colchicine regimen is now the FDA-approved standard, implying that the FDA evaluation of the dame data gave a conclusion distinct fro m that of the AHRQ. Since colchicine has such a narrow therapeutic window, and potentially major toxicity including death in acute and prolonged use, the AHRQ summary evaluation should be reconsidered.	We are not sure how to respond to this comment. In the evidence report we stated that "low dose colchicine is as effective as higher dose for reducing pain, with fewer side effects" and judged this as moderate strength evidence based on the one RCT, with between 52 and 74 patients randomized to one of the three treatment arms. We would not normally consider this to be a "large" trial, and since there is only one such study we judged this as moderate strength evidence. We don't see how this description of the evidence or SoE grade can be considered "harmful" to quality of care".

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Takeda Pharmaceuticals	General	Takeda Pharmaceuticals USA, Inc. appreciates the opportunity to review and submit comments to the Agency of Healthcare Research and Quality (AHRQ) Effective Healthcare Program regarding the draft report titled Management of Gout. As one of the world's leading pharmaceutical companies, we are committed to improving the health of people through leading innovation in medicine. We seek to bring new therapies to patients through a pipeline that includes compounds in development for gastroenterology, oncology, neurology, cardiovascular/metabolic disorders, rheumatology, and immunology/vaccines. Takeda's portfolio includes two compounds used in the management of gout, Colcrys (colchicine, USP) and Uloric (febuxostat). Colchicine is used for the prophylaxis and treatment of gout flares in adults. Febuxostat is a xanthine oxidase inhibitor and reduces serum uric acid levels for chronic gout patients who require long-term pharmacotherapy. We recognize the importance of having the most current information and data referenced in the AHRQ management of gout systematic review. Given our experience in this therapeutic area, we are submitting a comment to provide updates, since our submission in February 2014, regarding Colcrys and Uloric. For additional informational needs, please contact Deborah Walter, Federal Health Policy Director, at (202) 649-4009.	We have looked through the list of references provided and have accounted for all of the studies mentioned. We have added data for harms.